AF/$ 1642

USSN: 08/349,489
Dkt. No.: PP0999.004
2300-0999

PATENT

CERTIFICATE OF MAILING PURSUANT TO 37 CFR § 1.8

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11/12/2003 Michelle Hobson

Date Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: A. Hollerhan
RING	Group Art Unit: 1642
Serial No.: 08/349,489	Confirmation No.: 6479
Filing Date: December 2, 1994	Customer No.: 20855
Title: METHOD OF PROMOTING AN IMMUNE RESPONSE WITH A BISPECIFIC ANTIBODY	

APPEAL BRIEF TRANSMITTAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

Further to the Notice of Appeal filed June 13, 2003, transmitted herewith for filing in the above-identified patent application is an Appeal Brief ***in triplicate***, a Petition for Extension of Time, a check for $1280.00 ($330.00 – Appeal Brief fee and $950.00 – three month extension fee) and a return receipt postcard.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648.

Respectfully submitted,

Date: November 12, 2003

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BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

INTRODUCTION

Appellant submits in triplicate his brief on appeal in accordance with 37 C.F.R. §1.192. All claims were finally rejected under 35 U.S.C. § 112, first paragraph (enablement), as well as under 35 U.S.C. § 103(a) in the Final Office Action, mailed December 18, 2002. A Response After Final was filed on March 18, 2003 and a Notice of Appeal was filed June 13, 2003, making a Brief on Appeal due on or before August 13, 2003. Appellant requests a three-month extension of time and attach the appropriate

fee, making a response due on or before November 13, 2003. Accordingly, this Brief is timely filed. Appellant respectfully requests that the decision of the Examiner be reversed and that the claims on appeal proceed to allowance.

TABLE OF CONTENTS

INTRODUCTION 1

I. REAL PARTY IN INTEREST 5

II. RELATED APPEALS AND INTERFERENCES 5

III. STATUS OF THE CLAIMS 5

IV. STATUS OF THE AMENDMENTS 5

V. SUMMARY OF THE CLAIMS 6

VI. ISSUES ON APPEAL 7

VII. GROUPING OF CLAIMS 7

VIII. ARGUMENTS 9

1. Undue Experimentation is not required to practice the claimed invention throughout their scope 9

(a) The specification enables the claimed methods throughout their scope 9

(b) The specification enables the of use bispecific antibodies other than 2B1 12

(c) The references do not establish unpredictability 14

(d) Declaratory evidence of record has not been properly considered. 16

2. *Prima facie* obviousness of claims 1-3, 8 and 15 has not been established 18

(a) The references do not teach or suggest that a bispecific antibody could be used to induce antibodies to cancer antigens 19

(b) Declaratory evidence of record has not been properly considered 22

3. While *prima facie* obviousness has not been established, additional factual evidence of record further supports the nonobviousness of the claimed methods 23

4. Additional Arguments Regarding Separately-Grouped Claims 24

CONCLUSION 25

APPENDIX A: LIST OF CLAIMS ON APPEAL

I. REAL PARTY IN INTEREST

Chiron Corporation, the assignee of record of the above-referenced patent application is the real party in interest in this matter.

II. RELATED APPEALS AND INTERFERENCES

Appellant is not aware of any related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 1-3, 8 and 15 are currently pending in the above-referenced case (hereinafter "the application"). The application was originally filed on December 2, 1994 with claims 1-15. Subject to a Restriction Requirement, claims 4 and 9-14 were withdrawn from consideration. A CPA was filed on May 11, 1999 and, on June 18, 1999, Appellant amended claim 6. An *In re Katz* Declaration was filed on December 22, 1999, removing various references. In an Amendment after Final, filed August 23, 2001, claim 1 was amended and claims 5-7 were canceled, without prejudice or disclaimer. A second CPA was filed on December 18, 2001 requesting entry of these amendments. In an amendment filed September 9, 2002, claim 1 was amended into its current form. No claims were amended in the Response filed After Final on March 18, 2003. Therefore, claims 1, 2, 3, 8 and 15 are pending as shown in Appendix A. All pending claims remain rejected under 35 U.S.C. § 112, first paragraph and under 35 U.S.C. § 103.

IV. STATUS OF THE AMENDMENTS

In response to the Examiner's Final Office Action mailed December 18, 2002, Appellant filed an Amendment After Final with an accompanying (unsigned) Rule 132 Declaration by Dr.

Justin Wong on March 18, 2003. The claims were not amended at this time and a signed copy of Dr. Wong's Declaration was submitted April 1, 2003. An Advisory Action has not been received. Thus, the pending claims are as set forth in Appendix A and all pending claims remained rejected for the reasons set forth in the Final Office Action.

V. SUMMARY OF THE CLAIMS

Appellant's claims are drawn generally to a method of inducing production of antibodies against a cancer antigen (page 6, lines 24-28). In particular, the method comprises administering a bispecific antibody, *i.e.*, an antibody that recognizes two antigens, to a patient in an amount sufficient to induce production of antibodies to the second antigen of the bispecific antibody (page 5, lines 19-20). Furthermore, the bispecific antibody used in these methods includes a first binding site capable of recognizing and binding FcγRIII and a second binding site capable of recognizing and binding a second antigen (page 6, lines 24-28). The second antigen (recognized by the second binding site of the bispecific antibody) is a cancer antigen, particularly c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein or an antigen recognized by a monoclonal antibody produced by any of the following hybridomas: ATCC Accession Nos HB 11830, HB 11769, HB 11768, HB 10798, HB 10802, HB 8490, HB 8485, HB 8691, HB 11052, HB 10812, HB 8486, HB 10789, HB 8488, HB 8662, HB 8697, HB 10785, HB 10796, HB 10793, HB 11752, HB 10795, HB 10801, HB 11751 and HB 10794 (page 5, line 27 to page 6, line 1; page 19, lines 11-23). In addition, the second binding site of the bispecific antibody comprises a binding site derived from a monoclonal antibody produced by a hybridoma selected from the group consisting of: HB11830, 452F2 (HB 10811), 741F8 (HB 10807), 759E3 (HB 10808), 454C11 (HB 8484), 387H9 (HB 10802), 113F1 (HB 8490), 317G5 (HB 8485, HB 8691), 34F2 (HB 11052), 650E2 (HB 10812), 35E6 (HB 11769), 266B2 (HB 8486), 106A10 (HB 10789), 260F9 (HB 8488 and HB 8662), 33F8 (HB 8697), 9C6 (HB 10785), 35E10 (HB 10796), 140A7 (HB 10798), 36H3 (HB11768), 788G6 (HB 8692), 200F9 (HB 10791), 697B3 (HB 10806), 120H7 (HB 10790), 203E2 (HB 10799), 254H9 (HB 10792), 245E7 (HB 8489), 2G3 (HB 8491),

369F10 (HB 8682), 15D3 (HB 11342), 421E8 (HB 10793), 310B7 (HB 11752), 32A1 (HB 10795), 219F3 (HB 10801), 42E7 (HB 11751), and 388D4 (HB 10794) (page 6, lines 1-11).

In addition, the first binding site (FcγRIII) can be, for example, a binding site derived from the monoclonal antibody produced from the 3G8 hybridoma (page 16, lines 13-16). Additionally, the second antigen can be present in the patient (page 5, lines 25-26) or, alternatively, not present in the patient upon first administration of the bispecific antibody (page 6, lines 20-21). The bispecific antibody used in these methods can be produced by the hybrid hybridoma CRL 10197 (page 20, lines 23-24).

Thus, the present claims methods of inducing an immune response to a cancer antigen by administering a bispecific antibody, where the second binding site of the bispecific antibody recognizes the cancer antigen (page 5, lines 19-24).

VI. ISSUES ON APPEAL

1. Whether the specification adequately enables the claims on appeal under the provisions of 35 U.S.C. § 112, first paragraph.

2. Whether the claims on appeal are obvious over Hsieh-Ma et al. (Cancer Research, 1992) or Weiner et al. (Cancer Research, 1993) or Ring et al. (Breast Epithelial Antigens, 1991) in view of Fanger et al. (Critical Reviews in Immunology, 1992) or Snider et al. (J. Exp. Med. 171:1957-1963, 1990).

VII. GROUPING OF CLAIMS

Claims 1, 2, 3, 8 and 15 are separately patentable, enabled and described by the application as filed. Therefore, these claims are divided into 5 separate groups:

(1) Claim 1: Independent claim 1 is directed to a method of inducing production of antibodies against a cancer antigen by administering a bispecific antibody to a subject. The

bispecific antibody comprises two binding sites -- one that recognizes FcγRIII and the other that recognizes a cancer antigen. The second binding site (and second antigen recognized by the second binding site) is further defined in terms of Accession Numbers and other identifiers.

(2) Claim 2: Claim 2 is directed to the method of claim 1 and further specifies that the first binding site of the bispecific antibody is derived from the monoclonal antibody produced from the 3G8 hybridoma.

(3) Claim 3: Claim 3 is directed to the method of claim 1 and further specifies that the second (cancer) antigen is present in the patient.

(4) Claim 8: Claim 8 is directed to the method of claim 1 and further specifies that the bispecific antibody is produced by the hybrid hybridoma CRL 10197.

(5) Claim 15: Claim 15 is directed to the method of claim 1 and further specifies that the second (cancer) antigen is not present in the patient upon first administration of the bispecific antibody.

VIII. ARGUMENTS

1. Undue Experimentation is not required to practice the claimed invention throughout their scope

The claims have been rejected as not enabled by the specification. Appellant submits that undue experimentation is not required to practice the claimed invention because the claims are enabled throughout their scope and, in addition, that the references cited as allegedly establishing unpredictability do no such thing. Moreover, the Examiner has improperly ignored declaratory evidence establishing that the disclosure, as filed, thoroughly enables the claimed invention.

(a) The specification enables the claimed methods throughout their scope

The Examiner has continued to allege that the specification does not enable one of skill in the art to practice the methods as claimed. The Examiner's position remains that:

> ...the specification, while being enabling for the bispecific antibody 2B1 and methods of inducing an immune response by administering the antibody, does not reasonably provide enablement for methods of inducing an immune response using any bispecific antibody which binds FcγRIII and c-erbB-2 where the arm that binds c-erbB2 is "derived from" any of the numerous monoclonal antibodies recited in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. (Final Office Action, page 3).

Thus, the Examiner continues to assert that the claims must be limited to methods using the hybridoma (2B1) set forth in the working examples disclosed in the specification. (*See,* Final Office Action, page 3).

Appellant submits that there is ample guidance in the specification regarding bispecific antibodies as set forth in independent claim 1 and use of these antibodies in the claimed methods. As such, the enablement requirement of 35 U.S.C. § 112, first paragraph has been satisfied.

As a threshold matter, Appellant notes that the claims are not drawn to methods using any and all bispecific antibodies to induce any and all immune response. In fact, as noted above in

the Summary of the Invention, each and every one of the pending claims requires that the bispecific antibody be directed to FcγRIII and a specified cancer antigen. (*See*, Summary above and Appendix A). Furthermore, each and every one of the claims requires that administration of the precisely defined bispecific antibodies result in the induction of antibodies to the cancer antigen in the patient. Therefore, the scope of the claims is not as broad as painted by the Examiner.

In addition to misrepresenting the scope of the claimed invention, Appellant also submits that the Examiner has not applied the proper legal standard of enablement in maintaining this rejection and, moreover, has improperly ignored additional evidence of record. Indeed, it is axiomatic that evidence as to the availability of techniques for discovering additional embodiments is entirely relevant to the enablement inquiry. (*See, e.g.,* M.P.E.P. § 2164.01 which states the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art, citing *United States v. Telectronics Inc.,* 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989)). Routine experimentation is not "undue" and does not establish non-enablement. (see, *e.g., In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988), citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976). The Office must consider evidence provided by the applicant that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See, e.g.,* PTO Training Manuals on Enablement, page 42; MPEP 716.09; *In re Brandstadter,* 179 USPQ 286 (CCPA 1973); *In re Ambruster,* 185 USPQ 152 (CCPA 1975); and *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). The evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art. PTO Training Manual on Enablement, page 42.

An applicant is under no legal obligation to exemplify each and every member of a claimed genus. Rather, for a claimed genus, representative examples together with a statement applicable to the genus as whole is sufficient to establish enablement if the skilled artisan would expect the claimed genus could be used in the manner set forth. *See, e.g.,* U.S. Patent and

Trademark Office's Training Materials on Enablement, p. 29. Simply put, the proper legal standard for determining enablement is whether the specification provides enough guidance as to the existence of methods and materials that allow one of skill in the art to practice the claimed invention without undue experimentation. (see, *e.g., In re Wands,* 8 USPQ2d at 1404, citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976)).

The present record plainly establishes one of skill in the art could practice the claimed invention without undue experimentation. The specification is replete with representative examples and statements applicable to the genus as a whole. In particular, Appellant plainly teaches how to identify and use bispecific antibodies that bind to FcγRIII and a cancer antigen, as recited in the claimed methods. Indeed, the Examiner has acknowledged enablement of the exemplified embodiment (*e.g.,* use of 2B1 to induce antibodies to a cancer antigen), for example, on page 2, of the Final Office Action. Thus, the application discloses that bispecific antibodies were known and had been used to induce local cellular immune responses. (Background). In addition, methods of making bispecific antibodies were also known. (*See*, for example, page 9 of the specification and pages 17-20 describing cancer antigens). Moreover, methods of administering bispecific antibodies to a subject are clearly disclosed, for example, on page 24 of the application. Furthermore, with respect to determining whether antibody responses to the cancer antigen are induced, such methods were both routine at the time of filing and disclosed in the specification, for instance in the Examples.

Appellant's specification also contains the requisite statements applicable to the genus as a whole to satisfy the enablement requirement, on, for example, page 6, lines 24-28, where the application states that "[i]t has now been found that administration of bispecific antibodies which recognize and bind FcγRIII and a second antigen can promote an immune response in humans to the second antigen" and in Example 3, where it states "[t]his example demonstrates the induction of an immune response by administration of a bispecific antibody such as 2B1." Thus, in light of Appellant's disclosure (including the state of the art at the time of filing), designing, making and using bispecific antibodies that recognize FcγRIII and a cancer antigen to elicit antibody

production is well within the purview of a skilled artisan. The claims are fully enabled the specification and Appellant respectfully submits that the rejection of the pending claims under section 112, first paragraph should be removed.

Dr. Wong, an immunologist working in the field of bispecific antibodies, reviewed Appellant's specification and claims on appeal and unequivocally concluded that the claims were not unduly broad and, in fact, the specification provided ample guidance to the skilled worker to practice the methods as claimed:

> 7. In December 1994, the quantity of experimentation required to make bispecific antibodies that recognized FcγRIII and a cancer antigen was quite low. At the time of filing and as described in the specification, FcγRIII was a well-characterized isoform of the CD16 cell surface receptor. (*See,* for example, page 10, lines 6-16). One working in this field could have readily selected suitable cancer antigens, for example as described in detail on pages 17-20. Also well known at the time of filing were techniques of producing bispecific antibodies and these standard procedures are described throughout the specification as filed, for example, on page 9, line 12-28 (including the references cited therein). Based on these extensive teachings regarding each of the antigens recognized by the claimed bispecific antibody and, additionally, the extensive teachings regarding production of bispecific antibodies, it is evident that a skilled worker would have easily produced bispecific antibodies which bound both FcγRIII and a cancer antigen. Thus, it is clear from the specification that 2B1 is merely one example of a hybrid hybridoma capable of producing bispecific monoclonal antibody. Therefore, it is my opinion that it would have required only routine experimentation for the skilled worker to make a bispecific antibody that recognized FcγRIII and a cancer antigen, as recited in the pending claims.

Thus, the specification's disclosure fully enables the claims on appeal throughout their scope.

(b) The specification enables the use bispecific antibodies other than 2B1

As noted above, the Examiner continues to assert that it would require undue experimentation to practice the claimed methods with any bispecific antibody except 2B1. (Final Office Action, page 3).

Appellant submits that the factual record makes it plain that 2B1 is an exemplary bispecific antibody, and, in view of the broad disclosure of the specification, the claims cannot be limited to the bispecific antibody exemplified in the application. It is axiomatic that working examples are never required to establish enablement. *See, In re Stahilevitz* 212 USPQ 561 (CCPA 1982), in which the CCPA held that broad claims to immunological methods were enabled by the specification as filed despite not disclosing even a single operative embodiment. Even in the chemical arts, an applicant is never required to exemplify multiple embodiments encompassed by the claims. *See, e.g., In re Angstadt,* 190 USPQ 214 (CCPA 1976). Here, the Examiner is improperly requiring the Appellant show, *a priori*, that every species disclosed in the specification is operable. This is not the proper test of enablement. Simply put, the enablement requirement of Section 112 cannot be used as a justification for limiting Appellant to the embodiments disclosed in the working examples, particularly in light of the fact that the specification describes, with specificity and detail, bispecific antibodies to be used in the claimed methods.

Furthermore, the notion that one of ordinary skill in the art must have reasonable assurance of obtaining an active claimed product has been emphatically rejected by the courts. *See, Angstadt* at 219. So long as it is clear that some species render a composition operative, the inclusion of some possible inoperative species does not invalidate the claim under paragraph 1, of 35 U.S.C. §112. *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, CCPA 1971; *Horton v. Stevens*, 7 USPQ2d 1245, 1247, Fed. Cir. 1988. Moreover, even evidence of the need for some experimentation does not invalidate a claim on ground of undue experimentation, nor does it fulfill the PTO's burden of proof. (*In re Angstadt* at 504; *In re Morehouse*, 545 F.2d 162, 165, 192 USPQ 29,32, CCPA 1976.)

For the reasons set forth above, including the routine nature of making bispecific antibodies and the detailed disclosure of the specification (including working examples), it is clear that one of ordinary skill in the art could practice the claimed methods of anti-cancer

antigen antibody induction using any of the particularly claimed bispecific antibodies (FcγRIII- and cancer antigen-specific), without undue experimentation.

Again, Dr. Wong in full agreement that the claims should not be limited to 2B1:

> 8. Furthermore, the specification provides working examples and additional significant direction for evaluating whether a FcγRIII-cancer antigen binding bispecific antibody could be used to elicit an antibody response to the cancer antigen. Those of us working in the field of bispecific antibodies are well versed in administration of antibodies and in the various tests for determining whether antibodies are elicited, for example using assays described on pages 24-29 of the specification. Examples present in the specification demonstrate such assays. (See, Examples 2 and 3). Furthermore, since preparing bispecific antibodies in December of 1994 was well within the purview of a skilled worker, even if a particular bispecific antibody were inoperable for some reason (*e.g.*, it did not elicit antibodies against the cancer antigen), the skilled worker would have readily used the molecule as a starting point in order to design bispecific antibodies with the desired characteristics.

In sum, the application as filed provides ample guidance regarding all the claimed elements. Accordingly, it would have been plain to the skilled artisan that Appellants was in possession of the claimed subject matter at the time the application was filed.

(c) The references do not establish unpredictability

In the Final Office Action, the Examiner also continued to assert that various references (Rudikoff, Adair and Panka) demonstrate the "unpredictability" of the claimed methods. *See,* page 5 of the Final Office Action. In citing these references, the Examiner asserted, "the specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claimed." (See, page 5, Final Office Action). The Examiner's position appears to be that, due to recognized variability of CDRs, the claimed methods are unpredictable.

Enablement and predictability are determined as of the time of filing. Here, Rudikoff was published 12 years prior to Appellant's filing date; Adair 3 years prior; and Panka 6 years prior. Thus, none of these references are indicative of the state of the art in December 1994, the time this application was filed. Indeed, patents directed to production of bispecific antibodies

have routinely issued by the Office. (*See, e.g.,* U.S. Patent No. 4,474,893, cited on page 9, line 20 of the specification). Thus, contrary to the Examiner's assertion, at the time the pending application was filed, many of the problems associated with production of antibodies had been solved and these solutions were publicly available.

Even assuming, for the sake of argument only, that Rudikoff, Adair and/or Panka were representative of the state of the art as of Appellant's filing date, these references do not in any way establish unpredictability of methods involving the claimed bispecific antibodies to produce antibodies. In fact, none of these references address using bispecific antibodies at all, let alone using the particularly claimed bispecific antibodies to induce production of an antibody response. These references are a far cry away from establishing that the claimed methods are not enabled by Appellant's specification.

Thus, Rudikoff, Adair and Panka are not indicative of the state of the art at the time of filing and, moreover, are silent as to bispecific antibodies entirely. Therefore, these reference cannot serve as evidence that it would require undue experimentation to practice the invention as claimed. Discussions about CDRs in different antibodies does not rise to the level of establishing that the claimed invention is "unpredictable" or that it would require "undue experimentation" to practice the invention.

Dr. Wong also addressed Adair, Rudikoff and Panka and concluded that these references were not relevant to the claims on appeal:

> 9. It is further my opinion that Rudikoff, Adair or Panka do not accurately reflect the state of research in the field of bispecific antibodies as of December 1994. I base this opinion on the following facts. First, these references do not in any fashion address bispecific antibodies as used in the claimed methods. Rudikoff and Panka address how single amino acid substitutions in the CDR of an antibody can alter binding. Adair is directed to humanized antibody molecules (HAMs) having specificity for carcinoembryonic antigen (CEA) and to processes for their production using recombinant DNA technology. (See, Abstract). Nothing in these references is relevant to the claimed methods. Further, as all these references were published at least 3 years prior to December 1994, they are not representative of the state of the art at the time of filing.

In sum, the claimed methods are enabled by the specification as filed, and, accordingly, the various references cited by the Office are not relevant to the claimed invention and certainly do not establish unpredictability of the claimed methods.

(d) Declaratory evidence of record has not been properly considered

Despite the Office's failure to establish a *prima facie* case of non-enablement, Appellant has submitted still further evidence establishing that the specification fully enables the pending claims throughout their scope. The Office must consider evidence provided by the applicant that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See, e.g.,* PTO Training Manuals on Enablement, page 42; MPEP 716.09; *In re Brandstadter,* 179 USPQ 286 (CCPA 1973); *In re Ambruster,* 185 USPQ 152 (CCPA 1975); and *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). The evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art. PTO Training Manual on Enablement, page 42. In *In re Alton,* 37 USPQ2d 1578 (CAFC 1996), the Court of Appeals for the Federal Circuit held that it was error for the Examiner to dismiss with conclusory statements not only factual statements but also statements of opinion presented in Declarations made by qualified persons of ordinary skill in the art. The court commented that they were "aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner. [citation omitted]." *In re Alton,* 37 USPQ2d 1578 at 1583 n10.

In the present case, the Examiner has not considered the Declaratory evidence. In fact, Dr. Wong's Declaration completely rebuts the Examiner's conclusions that the claims on appeal are not enabled by the specification and that these claims are obvious over the cited references. Specifically, Dr. Wong notes the following facts and arrives at his conclusions using these facts.

First, bispecific antibodies as set forth in the claims (recognizing FcγRIII and a cancer antigen) were known at the time specification was filed. In particular, FcγRIII was a well-characterized isoform of the CD16 cell surface receptor. Similarly, a skilled artisan could have readily selected any suitable cancer antigen disclosed in the specification for use as the second

arm of the bispecific antibody. 2B1 is merely one example of a hybrid hybridoma capable of producing bispecific monoclonal antibody. *See,* Wong Declaration, paragraph 7, also citing page 10, lines 6-16 of the specification).

Second, it was known at the time of filing how to make bispecific antibodies and the specification also provides guidance in this regard. *See,* Wong Declaration, paragraph 7, citing page 9, line 12-28 of the specification.

Third, it was known how to administer bispecific antibodies to a subject. In addition, it was known how to test the subject to determine whether antibodies to the cancer antigen were elicited. *See,* Wong Declaration, paragraph 8.

On the basis of the foregoing, factual statements (further supported by references), Dr. Wong concludes that a skilled worker could have readily designed, made, tested and used a bispecific antibody falling within the scope of the claims:

> 10. Thus, it is my opinion that a skilled worker could have readily designed, made, tested and used a bispecific antibody falling within the scope of the claims. As noted above, bispecific antibodies were routinely made and administered. Similarly, assays for testing antibody production were routine in December 1994. The generation and testing of bispecific antibodies is described in Fanger et al. (1991) *Trends Biotechnol* 9(11):375-80 (Exhibit B) and Ring et al. "Breast Epithelial Antigens: Molecular Biology to Clinical Applications" (Exhibit C), as well as U.S. Patent Nos. 4,714,681 and 4,474,893 (Exhibit D). These and other references address the pertinent question at issue here -- whether bispecific antibodies that recognize FcγRIII and a cancer antigen can be made and used to produce antibodies against the cancer antigens following the teachings of the specification. These references plainly confirm that neither making bispecific antibodies nor testing antibody production in response to administration of these antibodies were unpredictable as of December 1994. Further, they are clearly representative of the high level of existing skill in the art and the fact that generation of bispecific antibodies was considered routine and entirely predictable in December 1994. In sum, to the skilled worker, making and using the claimed bispecific antibodies would have been routine and would have required little or no experimentation, particularly in light of the clear guidance in the specification regarding how to make, test and use bispecific antibodies as claimed.
>
> 11. In view of the foregoing facts regarding the routine nature of experimentation required to make, use and deliver bispecific antibodies directed against FcγRIII and a cancer antigen, the extensive direction provided by the

> specification, the straightforward nature of the claimed subject matter, the high level of the skilled worker, the sophistication of the art, and the predictability of the art, it is my unequivocal opinion that the specification enabled, in December 1994, a skilled worker to practice the methods as claimed.

Based on the teachings of the specification and the state of the art at the time of filing, Dr. Wong confirms that it would have required little or no experimentation for one skilled in the art to identify suitable bispecific antibodies and evaluate these antibodies for their ability to generate antibodies against a cancer antigen. (See, Wong Declaration, paragraphs 7-10).

Thus, the evidence of record conclusively contradicts the Examiner's assertions that it would have required undue experimentation to practice the claimed methods using antibodies other than 2B1. Accordingly, Appellant submits that the enablement rejections should be withdrawn.

2. *Prima facie* obviousness of claims 1-3, 8 and 15 has not been established

Claims 1-3, 8 and 15 were rejected under 35 U.S.C. § 103(a) (hereinafter "103") as allegedly obvious over Hsieh-Ma et al. (Cancer Research, 1992) or Weiner et al. (Cancer Research, 1993) or Ring et al. (Breast Epithelial Antigens, 1991) in view of Fanger et al. (Critical Reviews in Immunology, 1992) or Snider et al. (J. Exp. Med. 171:1957-1963, 1990). Collectively, Hseih-Ma, Weiner and Ring are referred to as the "primary references." In addition, claims 1-3, 5-8, and 15 also stand rejected as allegedly obvious over the primary references in view of Fanger or Snider and in further view of U.S. Patent No. 6,054,561.

In support of the rejections, the Examiner maintained that the primary references teach all the limitations of the claims except for antibody production to the second antigen. (Final Office Action, paragraph 6, page 6). Fanger and Snider were cited for alleging teaching that bispecific antibodies targeted to the APC cell antigens induce production of antibodies to the second antigen. (Final Office Action, paragraph 6, page 6). Further, in rejecting Appellant's previous arguments the Final Office Action stated:

> the burden of proof is upon Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibodies with the antibody and the 2B1 antibody of the prior art.

Appellant submits the Examiner has used prohibited hindsight reconstruction in making these rejections, as there is no teaching, suggestion or motivation within the cited references to support the rejection made by the Examiner. Additionally, the claims are patentable because of secondary considerations of non-obviousness.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The reference must teach all the limitations of the claimed invention and, moreover, suggests the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of along sought and difficult scientific goal was obvious" and *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.") Thus, the Board has previously acknowledged that disclosure of an isolated protein does not necessarily render obvious the same recombinantly produced protein. *See, e.g., Ex parte Goeddel,* 5 USPQ2d 1449 (BAPI, 1987).

Appellant submits that the Examiner has failed to make out a *prima facie* case of obviousness because no combination of the references teaches or suggests each and every element of the invention recited in claims 1, 3, 8 and 15. Further, there is simply no motivation within the references to arrive at the claimed invention.

(a) The references do not teach or suggest that a bispecific antibody could be used to induce antibodies to cancer antigens

To briefly reiterate, claims 1-3, 8 and 15 are all directed to methods of inducing **antibodies** to cancer antigens by administering the bispecific antibodies as claimed. Nowhere do

any of the references teach or suggest the induction of antibodies against cancer antigens using bispecific antibodies as claimed. Nor do these references provide any motivation or suggest the desirability of such methods. The failure of the cited references to suggest the claimed methods is also laid out in the Wong Declaration of record. There is simply no basis in the references for making an obviousness rejection and Appellant submits that it should be withdrawn.

Turning now to the Examiner's assertion that the burden in on Appellant to show that 2B1 bispecific antibody (disclosed in some of the references) would not have inherently induced antibodies to cancer antigens as claimed, Appellant submits that this is not the proper standard for determining obviousness. Indeed, it is well settled that, obviousness **cannot** be predicated on what is unknown:

> The inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. *In re Shetty, supra* quoting *In re Sporman,* 150 USPQ 449 (CCPA 1966).

In the pending case, it was certainly not known at the time of filing that the claimed bispecific antibodies would induce antibodies against cancer antigens. Dr. Wong is in accord:

> 12. It is further my opinion that the references cited in the Final Office Action do not describe, demonstrate or suggest the claimed methods. The application at issue discloses and claims methods of inducing an antibody response to a cancer antigen using a bispecific antibody. The bispecific antibody itself recognized FcγRIII and the cancer antigen. There is no disclosure in any of Hseih-Ma, Weiner, Ring, Fanger of Snider that would lead any scientist working in this area to conclude that bispecific antibodies would be useful in generating antibodies against cancer antigens. The fact that bispecific antibodies can have induce such antibodies was, in fact, a surprising finding made by the present inventors *after* all of the references were published, as noted on page 6, lines 24-28 of the specification:
>
> > It has now been found that administration of bispecific antibodies which recognize and bind FcγRIII and a second antigen can promote an immune response in humans to the second antigen. The immune response includes the formation of antibodies to the second antigen.

> Nowhere do any of the references report or test antibody production in response to the precisely-claimed subject matter. Accordingly, I do not believe that any combination of the cited references would lead one of skill in the art to the methods claimed by Applicant.

Thus, the Examiner has improper ignored the requirement that the claimed methods result in the induction of antibodies to the cancer antigen recognized by the second binding site of the bispecific antibody. Functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. (M.P.E.P. 2173.05(g) Functional Limitations, Eighth Edition). There is nothing inherently wrong with defining some part of an invention in functional terms and functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). Indeed, where the particular intended result (in this case production of antibodies to specified antigens) is a limitation of the pending claims it is entirely relevant to patentability. Accordingly, the requirement in these claims regarding the nature of immune response generated is entirely relevant the obviousness inquiry and establishes, along with the other evidence of record, that the claims are patentable over any combination of the cited references.

Here, the claims on appeal expressly recite that the claimed methods must result in the production of antibodies directed against the cancer antigen and, hence, this limitation is relevant to patentability. It is unacceptable for the Examiner to ignore this limitation and assert that any art related to the making or using of bispecific antibodies is relevant, much less than these references render the particularly claimed invention unpatentable. Likewise, the Examiner cannot ignore the legal axiom that obviousness cannot be based on what was allegedly inherent. Thus, when the proper legal standards of obviousness are applied, it is clear that the claimed methods, drawn to production of antibodies using bispecific antibodies, are in no way obvious over the cited references.

There is, in sum, no motivation provided by the cited references to arrive at methods of inducing antibodies to cancer antigens as recited in the appealed claims. The steps and results of

the claimed methods are precisely defined -- in the claims themselves, not in the references. None of the references teach that antibodies to cancer antigens would be induced by administration of the claimed bispecific antibodies. Therefore, Appellant respectfully requests that the rejection of these claims as allegedly obvious over the cited references be withdrawn, and that these claims be allowed.

(b) Declaratory evidence of record has not been properly considered

As with enablement, Appellant submits that the Declaration of Dr. Justin Wong has not been adequately considered with regard to obviousness. Indeed, Dr. Wong, an immunologist by training who works in the field of bispecific antibodies, concluded that the references cited by the Examiner did not render the pending claims unpatentable, stating that:

> 12. It is further my opinion that the references cited in the Final Office Action do not describe, demonstrate or suggest the claimed methods. The application at issue discloses and claims methods of inducing an antibody response to a cancer antigen using a bispecific antibody. The bispecific antibody itself recognized FcγRIII and the cancer antigen. There is no disclosure in any of Hseih-Ma, Weiner, Ring, Fanger of Snider that would lead any scientist working in this area to conclude that bispecific antibodies would be useful in generating antibodies against cancer antigens. ... Nowhere do any of the references report or test antibody production in response t22 the precisely-claimed subject matter. Accordingly, I do not believe that any combination of the cited references would lead one of skill in the art to the methods claimed by Applicant.

The Examiner has not adequately addressed this convincing factual evidence. When properly considered, Dr. Wong is yet another part of the factual record that conclusively contradicts the Examiner's assertions that any combination of the cited references renders the pending claims obvious.

3. While *prima facie* obviousness has not been established, additional factual evidence of record further supports the nonobviousness of the claimed methods

As discussed above and during prosecution of this application, the Examiner has not established the *prima facie* obviousness of the claimed methods because the cited references do not teach or suggest induction of an antibody response to the cancer antigen recognized by the second binding site of a bispecific antibody.

Since no *prima facie* case has been established, Appellant has no burden of coming forward with evidence positively establishing nonobviousness. *See, e.g., In re Rinehart* 189 USPQ 143 (CCPA 1976).

However, additional scientific evidence is in fact of record in the present case and that additional evidence further supports the nonobviousness of the presently claimed methods. For example, it is clear from the factual record that eliciting an antibody response to a cancer antigen was neither contemplated nor expected by those working in this field. As described in the specification:

> Thus far in research studying the efficacy of bispecific antibodies, localized tumor cell lysis has been observed in cellular and murine *in vivo* studies where the effector cells have been in close proximity to the tumor cells upon administration of the bispecific antibody. ...
>
> It has now been found that administration of bispecific antibodies which recognize and bind FcγRIII and a second antigen can promote an immune response in humans to the second antigen. The immune response includes the formation of antibodies to the second antigen. (page 5, lines 9-12 and page 6, lines 24-28 of the specification)

The Examples further indicate how the methods of the appealed claims result in unexpected production of antibodies to the cancer antigen. *See, e.g.,* Table 1 on page 27 of the specification.

In summary, although a *prima facie* case of obviousness has not been made out (and indeed the references contain no supporting basis), additional factual evidence or record in the present case lends even further support to the nonobviousness of the claimed methods.

4. Additional arguments regarding separately grouped claims

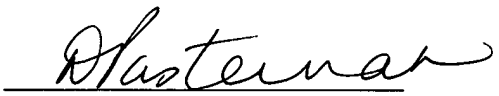
Each one of the preceding arguments is applicable to all of the separately grouped claims, *i.e.*, to each claim individually. For the sake of brevity, the arguments have been set out primarily as to independent claim 1. Claims 2-3, 8 and 15 contain all the elements of independent claim 1 and are, therefore, described, definite and patentable over the cited references for the reasons discussed in detail above. The dependent claims are also further limited in ways that are neither described nor suggested by the cited references, namely by further defining the elements of the claimed methods. The Examiner has not adequately explained why these claims are considered unpatentable over the cited references.

CONCLUSION

For the reasons stated above, Appellant respectfully submits that the pending claims are patentable over the art cited by the Examiner and, in addition, are described and sufficiently definite. Accordingly, Appellants request that the objections to the specification and the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: November 12, 2003

By: 

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CLAIMS ON APPEAL

1. (previously presented): A method of inducing production of antibodies against a cancer antigen, comprising the step of administering a bispecific antibody to the patient, said bispecific antibody comprising a first binding site capable of recognizing and binding a first antigen wherein said first antigen is FcγRIII and further comprising a second binding site capable of recognizing and binding a second antigen, in an amount sufficient to induce production of antibodies to said second antigen in said patient, wherein said second antigen is a cancer antigen selected from the group consisting of c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein and an antigen recognized by a monoclonal antibody produced by any of the following hybridomas: ATCC Accession Nos HB 11830, HB 11769, HB 11768, HB 10798, HB 10802, HB 8490, HB 8485, HB 8691, HB 11052, HB 10812, HB 8486, HB 10789, HB 8488, HB 8662, HB 8697, HB 10785, HB 10796, HB 10793, HB 11752, HB 10795, HB 10801, HB 11751 and HB 10794 and further wherein said second binding site comprises a binding site derived from a monoclonal antibody produced by a hybridoma selected from the group consisting of: HB11830, 452F2 (HB 10811), 741F8 (HB 10807), 759E3 (HB 10808), 454C11 (HB 8484), 387H9 (HB 10802), 113F1 (HB 8490), 317G5 (HB 8485, HB 8691), 34F2 (HB 11052), 650E2 (HB 10812), 35E6 (HB 11769), 266B2 (HB 8486), 106A10 (HB 10789), 260F9 (HB 8488 and HB 8662), 33F8 (HB 8697), 9C6 (HB 10785), 35E10 (HB 10796), 140A7 (HB 10798), 36H3 (HB11768), 788G6 (HB 8692), 200F9 (HB 10791), 697B3 (HB 10806), 120H7 (HB 10790), 203E2 (HB 10799), 254H9 (HB 10792), 245E7 (HB 8489), 2G3 (HB 8491), 369F10 (HB 8682), 15D3 (HB 11342), 421E8 (HB 10793), 310B7 (HB 11752), 32A1 (HB 10795), 219F3 (HB 10801), 42E7 (HB 11751), and 388D4 (HB 10794).

2. (original): The method according to claim 1, wherein said first binding site is a binding site derived from the monoclonal antibody produced from the 3G8 hybridoma.

3. (original): The method according to claim 1, wherein said second antigen is present in the patient.

4 to 7. (canceled).

8. (original): The method according to claim 1, wherein said bispecific antibody is produced by the hybrid hybridoma CRL 10197.

9 to 14. (canceled).

15. (original): The method according to claim 1, wherein said second antigen is not present in the patient upon first administration of the bispecific antibody.

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PATENT

CERTIFICATE OF MAILING PURSUANT TO 37 CFR § 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Appeal Brief – Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on November 12, 2003.

11/12/2003 Michelle Hobson

Date Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: A. Hollerhan
RING	Group Art Unit: 1642
Serial No.: 08/349,489	Confirmation No.: 6479
Filing Date: December 2, 1994	Customer No.: 20855
Title: METHOD OF PROMOTING AN IMMUNE RESPONSE WITH A BISPECIFIC ANTIBODY	

BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

INTRODUCTION

Appellant submits in triplicate his brief on appeal in accordance with 37 C.F.R. §1.192. All claims were finally rejected under 35 U.S.C. § 112, first paragraph (enablement), as well as under 35 U.S.C. § 103(a) in the Final Office Action, mailed December 18, 2002. A Response After Final was filed on March 18, 2003 and a Notice of Appeal was filed June 13, 2003, making a Brief on Appeal due on or before August 13, 2003. Appellant requests a three-month extension of time and attach the appropriate

fee, making a response due on or before November 13, 2003. Accordingly, this Brief is timely filed. Appellant respectfully requests that the decision of the Examiner be reversed and that the claims on appeal proceed to allowance.

TABLE OF CONTENTS

INTRODUCTION 1

I. REAL PARTY IN INTEREST 5

II. RELATED APPEALS AND INTERFERENCES 5

III. STATUS OF THE CLAIMS 5

IV. STATUS OF THE AMENDMENTS 5

V. SUMMARY OF THE CLAIMS 6

VI. ISSUES ON APPEAL 7

VII. GROUPING OF CLAIMS 7

VIII. ARGUMENTS 9

1. Undue Experimentation is not required to practice the claimed invention throughout their scope 9

(a) The specification enables the claimed methods throughout their scope 9

(b) The specification enables the of use bispecific antibodies other than 2B1 12

(c) The references do not establish unpredictability 14

(d) Declaratory evidence of record has not been properly considered. 16

2. *Prima facie* obviousness of claims 1-3, 8 and 15 has not been established 18

(a) The references do not teach or suggest that a bispecific antibody could be used to induce antibodies to cancer antigens 19

(b) Declaratory evidence of record has not been properly considered 22

3. While *prima facie* obviousness has not been established, additional factual evidence of record further supports the nonobviousness of the claimed methods 23

4. Additional Arguments Regarding Separately-Grouped Claims 24

CONCLUSION 25

APPENDIX A: LIST OF CLAIMS ON APPEAL

I. REAL PARTY IN INTEREST

Chiron Corporation, the assignee of record of the above-referenced patent application is the real party in interest in this matter.

II. RELATED APPEALS AND INTERFERENCES

Appellant is not aware of any related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 1-3, 8 and 15 are currently pending in the above-referenced case (hereinafter "the application"). The application was originally filed on December 2, 1994 with claims 1-15. Subject to a Restriction Requirement, claims 4 and 9-14 were withdrawn from consideration. A CPA was filed on May 11, 1999 and, on June 18, 1999, Appellant amended claim 6. An *In re Katz* Declaration was filed on December 22, 1999, removing various references. In an Amendment after Final, filed August 23, 2001, claim 1 was amended and claims 5-7 were canceled, without prejudice or disclaimer. A second CPA was filed on December 18, 2001 requesting entry of these amendments. In an amendment filed September 9, 2002, claim 1 was amended into its current form. No claims were amended in the Response filed After Final on March 18, 2003. Therefore, claims 1, 2, 3, 8 and 15 are pending as shown in Appendix A. All pending claims remain rejected under 35 U.S.C. § 112, first paragraph and under 35 U.S.C. § 103.

IV. STATUS OF THE AMENDMENTS

In response to the Examiner's Final Office Action mailed December 18, 2002, Appellant filed an Amendment After Final with an accompanying (unsigned) Rule 132 Declaration by Dr.

Justin Wong on March 18, 2003. The claims were not amended at this time and a signed copy of Dr. Wong's Declaration was submitted April 1, 2003. An Advisory Action has not been received. Thus, the pending claims are as set forth in Appendix A and all pending claims remained rejected for the reasons set forth in the Final Office Action.

V. SUMMARY OF THE CLAIMS

Appellant's claims are drawn generally to a method of inducing production of antibodies against a cancer antigen (page 6, lines 24-28). In particular, the method comprises administering a bispecific antibody, *i.e.,* an antibody that recognizes two antigens, to a patient in an amount sufficient to induce production of antibodies to the second antigen of the bispecific antibody (page 5, lines 19-20). Furthermore, the bispecific antibody used in these methods includes a first binding site capable of recognizing and binding FcγRIII and a second binding site capable of recognizing and binding a second antigen (page 6, lines 24-28). The second antigen (recognized by the second binding site of the bispecific antibody) is a cancer antigen, particularly c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein or an antigen recognized by a monoclonal antibody produced by any of the following hybridomas: ATCC Accession Nos HB 11830, HB 11769, HB 11768, HB 10798, HB 10802, HB 8490, HB 8485, HB 8691, HB 11052, HB 10812, HB 8486, HB 10789, HB 8488, HB 8662, HB 8697, HB 10785, HB 10796, HB 10793, HB 11752, HB 10795, HB 10801, HB 11751 and HB 10794 (page 5, line 27 to page 6, line 1; page 19, lines 11-23). In addition, the second binding site of the bispecific antibody comprises a binding site derived from a monoclonal antibody produced by a hybridoma selected from the group consisting of: HB11830, 452F2 (HB 10811), 741F8 (HB 10807), 759E3 (HB 10808), 454C11 (HB 8484), 387H9 (HB 10802), 113F1 (HB 8490), 317G5 (HB 8485, HB 8691), 34F2 (HB 11052), 650E2 (HB 10812), 35E6 (HB 11769), 266B2 (HB 8486), 106A10 (HB 10789), 260F9 (HB 8488 and HB 8662), 33F8 (HB 8697), 9C6 (HB 10785), 35E10 (HB 10796), 140A7 (HB 10798), 36H3 (HB11768), 788G6 (HB 8692), 200F9 (HB 10791), 697B3 (HB 10806), 120H7 (HB 10790), 203E2 (HB 10799), 254H9 (HB 10792), 245E7 (HB 8489), 2G3 (HB 8491),

369F10 (HB 8682), 15D3 (HB 11342), 421E8 (HB 10793), 310B7 (HB 11752), 32A1 (HB 10795), 219F3 (HB 10801), 42E7 (HB 11751), and 388D4 (HB 10794) (page 6, lines 1-11).

In addition, the first binding site (FcγRIII) can be, for example, a binding site derived from the monoclonal antibody produced from the 3G8 hybridoma (page 16, lines 13-16). Additionally, the second antigen can be present in the patient (page 5, lines 25-26) or, alternatively, not present in the patient upon first administration of the bispecific antibody (page 6, lines 20-21). The bispecific antibody used in these methods can be produced by the hybrid hybridoma CRL 10197 (page 20, lines 23-24).

Thus, the present claims methods of inducing an immune response to a cancer antigen by administering a bispecific antibody, where the second binding site of the bispecific antibody recognizes the cancer antigen (page 5, lines 19-24).

VI. ISSUES ON APPEAL

1. Whether the specification adequately enables the claims on appeal under the provisions of 35 U.S.C. § 112, first paragraph.

2. Whether the claims on appeal are obvious over Hsieh-Ma et al. (Cancer Research, 1992) or Weiner et al. (Cancer Research, 1993) or Ring et al. (Breast Epithelial Antigens, 1991) in view of Fanger et al. (Critical Reviews in Immunology, 1992) or Snider et al. (J. Exp. Med. 171:1957-1963, 1990).

VII. GROUPING OF CLAIMS

Claims 1, 2, 3, 8 and 15 are separately patentable, enabled and described by the application as filed. Therefore, these claims are divided into 5 separate groups:

(1) Claim 1: Independent claim 1 is directed to a method of inducing production of antibodies against a cancer antigen by administering a bispecific antibody to a subject. The

bispecific antibody comprises two binding sites -- one that recognizes FcγRIII and the other that recognizes a cancer antigen. The second binding site (and second antigen recognized by the second binding site) is further defined in terms of Accession Numbers and other identifiers.

(2) Claim 2: Claim 2 is directed to the method of claim 1 and further specifies that the first binding site of the bispecific antibody is derived from the monoclonal antibody produced from the 3G8 hybridoma.

(3) Claim 3: Claim 3 is directed to the method of claim 1 and further specifies that the second (cancer) antigen is present in the patient.

(4) Claim 8: Claim 8 is directed to the method of claim 1 and further specifies that the bispecific antibody is produced by the hybrid hybridoma CRL 10197.

(5) Claim 15: Claim 15 is directed to the method of claim 1 and further specifies that the second (cancer) antigen is not present in the patient upon first administration of the bispecific antibody.

VIII. ARGUMENTS

1. Undue Experimentation is not required to practice the claimed invention throughout their scope

The claims have been rejected as not enabled by the specification. Appellant submits that undue experimentation is not required to practice the claimed invention because the claims are enabled throughout their scope and, in addition, that the references cited as allegedly establishing unpredictability do no such thing. Moreover, the Examiner has improperly ignored declaratory evidence establishing that the disclosure, as filed, thoroughly enables the claimed invention.

(a) The specification enables the claimed methods throughout their scope

The Examiner has continued to allege that the specification does not enable one of skill in the art to practice the methods as claimed. The Examiner's position remains that:

> ...the specification, while being enabling for the bispecific antibody 2B1 and methods of inducing an immune response by administering the antibody, does not reasonably provide enablement for methods of inducing an immune response using any bispecific antibody which binds FcγRIII and c-erbB-2 where the arm that binds c-erbB2 is "derived from" any of the numerous monoclonal antibodies recited in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. (Final Office Action, page 3).

Thus, the Examiner continues to assert that the claims must be limited to methods using the hybridoma (2B1) set forth in the working examples disclosed in the specification. (*See,* Final Office Action, page 3).

Appellant submits that there is ample guidance in the specification regarding bispecific antibodies as set forth in independent claim 1 and use of these antibodies in the claimed methods. As such, the enablement requirement of 35 U.S.C. § 112, first paragraph has been satisfied.

As a threshold matter, Appellant notes that the claims are not drawn to methods using any and all bispecific antibodies to induce any and all immune response. In fact, as noted above in

the Summary of the Invention, each and every one of the pending claims requires that the bispecific antibody be directed to FcγRIII and a specified cancer antigen. (*See*, Summary above and Appendix A). Furthermore, each and every one of the claims requires that administration of the precisely defined bispecific antibodies result in the induction of antibodies to the cancer antigen in the patient. Therefore, the scope of the claims is not as broad as painted by the Examiner.

In addition to misrepresenting the scope of the claimed invention, Appellant also submits that the Examiner has not applied the proper legal standard of enablement in maintaining this rejection and, moreover, has improperly ignored additional evidence of record. Indeed, it is axiomatic that evidence as to the availability of techniques for discovering additional embodiments is entirely relevant to the enablement inquiry. (*See, e.g.,* M.P.E.P. § 2164.01 which states the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art, citing *United States v. Telectronics Inc.,* 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989)). Routine experimentation is not "undue" and does not establish non-enablement. (see, *e.g., In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988), citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976). The Office must consider evidence provided by the applicant that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See, e.g.,* PTO Training Manuals on Enablement, page 42; MPEP 716.09*; In re Brandstadter,* 179 USPQ 286 (CCPA 1973); *In re Ambruster,* 185 USPQ 152 (CCPA 1975); and *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). The evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art. PTO Training Manual on Enablement, page 42.

An applicant is under no legal obligation to exemplify each and every member of a claimed genus. Rather, for a claimed genus, representative examples together with a statement applicable to the genus as whole is sufficient to establish enablement if the skilled artisan would expect the claimed genus could be used in the manner set forth. *See, e.g.,* U.S. Patent and

Trademark Office's Training Materials on Enablement, p. 29. Simply put, the proper legal standard for determining enablement is whether the specification provides enough guidance as to the existence of methods and materials that allow one of skill in the art to practice the claimed invention without undue experimentation. (see, *e.g., In re Wands,* 8 USPQ2d at 1404, citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976)).

The present record plainly establishes one of skill in the art could practice the claimed invention without undue experimentation. The specification is replete with representative examples and statements applicable to the genus as a whole. In particular, Appellant plainly teaches how to identify and use bispecific antibodies that bind to FcγRIII and a cancer antigen, as recited in the claimed methods. Indeed, the Examiner has acknowledged enablement of the exemplified embodiment (*e.g.,* use of 2B1 to induce antibodies to a cancer antigen), for example, on page 2, of the Final Office Action. Thus, the application discloses that bispecific antibodies were known and had been used to induce local cellular immune responses. (Background). In addition, methods of making bispecific antibodies were also known. (*See*, for example, page 9 of the specification and pages 17-20 describing cancer antigens). Moreover, methods of administering bispecific antibodies to a subject are clearly disclosed, for example, on page 24 of the application. Furthermore, with respect to determining whether antibody responses to the cancer antigen are induced, such methods were both routine at the time of filing and disclosed in the specification, for instance in the Examples.

Appellant's specification also contains the requisite statements applicable to the genus as a whole to satisfy the enablement requirement, on, for example, page 6, lines 24-28, where the application states that "[i]t has now been found that administration of bispecific antibodies which recognize and bind FcγRIII and a second antigen can promote an immune response in humans to the second antigen" and in Example 3, where it states "[t]his example demonstrates the induction of an immune response by administration of a bispecific antibody such as 2B1." Thus, in light of Appellant's disclosure (including the state of the art at the time of filing), designing, making and using bispecific antibodies that recognize FcγRIII and a cancer antigen to elicit antibody

production is well within the purview of a skilled artisan. The claims are fully enabled the specification and Appellant respectfully submits that the rejection of the pending claims under section 112, first paragraph should be removed.

Dr. Wong, an immunologist working in the field of bispecific antibodies, reviewed Appellant's specification and claims on appeal and unequivocally concluded that the claims were not unduly broad and, in fact, the specification provided ample guidance to the skilled worker to practice the methods as claimed:

> 7. In December 1994, the quantity of experimentation required to make bispecific antibodies that recognized FcγRIII and a cancer antigen was quite low. At the time of filing and as described in the specification, FcγRIII was a well-characterized isoform of the CD16 cell surface receptor. (*See,* for example, page 10, lines 6-16). One working in this field could have readily selected suitable cancer antigens, for example as described in detail on pages 17-20. Also well known at the time of filing were techniques of producing bispecific antibodies and these standard procedures are described throughout the specification as filed, for example, on page 9, line 12-28 (including the references cited therein). Based on these extensive teachings regarding each of the antigens recognized by the claimed bispecific antibody and, additionally, the extensive teachings regarding production of bispecific antibodies, it is evident that a skilled worker would have easily produced bispecific antibodies which bound both FcγRIII and a cancer antigen. Thus, it is clear from the specification that 2B1 is merely one example of a hybrid hybridoma capable of producing bispecific monoclonal antibody. Therefore, it is my opinion that it would have required only routine experimentation for the skilled worker to make a bispecific antibody that recognized FcγRIII and a cancer antigen, as recited in the pending claims.

Thus, the specification's disclosure fully enables the claims on appeal throughout their scope.

(b) The specification enables the use bispecific antibodies other than 2B1

As noted above, the Examiner continues to assert that it would require undue experimentation to practice the claimed methods with any bispecific antibody except 2B1. (Final Office Action, page 3).

Appellant submits that the factual record makes it plain that 2B1 is an exemplary bispecific antibody, and, in view of the broad disclosure of the specification, the claims cannot be limited to the bispecific antibody exemplified in the application. It is axiomatic that working examples are never required to establish enablement. *See, In re Stahilevitz* 212 USPQ 561 (CCPA 1982), in which the CCPA held that broad claims to immunological methods were enabled by the specification as filed despite not disclosing even a single operative embodiment. Even in the chemical arts, an applicant is never required to exemplify multiple embodiments encompassed by the claims. *See, e.g., In re Angstadt,* 190 USPQ 214 (CCPA 1976). Here, the Examiner is improperly requiring the Appellant show, *a priori*, that every species disclosed in the specification is operable. This is not the proper test of enablement. Simply put, the enablement requirement of Section 112 cannot be used as a justification for limiting Appellant to the embodiments disclosed in the working examples, particularly in light of the fact that the specification describes, with specificity and detail, bispecific antibodies to be used in the claimed methods.

Furthermore, the notion that one of ordinary skill in the art must have reasonable assurance of obtaining an active claimed product has been emphatically rejected by the courts. *See, Angstadt* at 219. So long as it is clear that some species render a composition operative, the inclusion of some possible inoperative species does not invalidate the claim under paragraph 1, of 35 U.S.C. §112. *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, CCPA 1971; *Horton v. Stevens*, 7 USPQ2d 1245, 1247, Fed. Cir. 1988. Moreover, even evidence of the need for some experimentation does not invalidate a claim on ground of undue experimentation, nor does it fulfill the PTO's burden of proof. (*In re Angstadt* at 504; *In re Morehouse*, 545 F.2d 162, 165, 192 USPQ 29,32, CCPA 1976.)

For the reasons set forth above, including the routine nature of making bispecific antibodies and the detailed disclosure of the specification (including working examples), it is clear that one of ordinary skill in the art could practice the claimed methods of anti-cancer

antigen antibody induction using any of the particularly claimed bispecific antibodies (FcγRIII- and cancer antigen-specific), without undue experimentation.

Again, Dr. Wong in full agreement that the claims should not be limited to 2B1:

> 8. Furthermore, the specification provides working examples and additional significant direction for evaluating whether a FcγRIII-cancer antigen binding bispecific antibody could be used to elicit an antibody response to the cancer antigen. Those of us working in the field of bispecific antibodies are well versed in administration of antibodies and in the various tests for determining whether antibodies are elicited, for example using assays described on pages 24-29 of the specification. Examples present in the specification demonstrate such assays. (See, Examples 2 and 3). Furthermore, since preparing bispecific antibodies in December of 1994 was well within the purview of a skilled worker, even if a particular bispecific antibody were inoperable for some reason (*e.g.*, it did not elicit antibodies against the cancer antigen), the skilled worker would have readily used the molecule as a starting point in order to design bispecific antibodies with the desired characteristics.

In sum, the application as filed provides ample guidance regarding all the claimed elements. Accordingly, it would have been plain to the skilled artisan that Appellants was in possession of the claimed subject matter at the time the application was filed.

(c) The references do not establish unpredictability

In the Final Office Action, the Examiner also continued to assert that various references (Rudikoff, Adair and Panka) demonstrate the "unpredictability" of the claimed methods. *See,* page 5 of the Final Office Action. In citing these references, the Examiner asserted, "the specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claimed." (See, page 5, Final Office Action). The Examiner's position appears to be that, due to recognized variability of CDRs, the claimed methods are unpredictable.

Enablement and predictability are determined as of the time of filing. Here, Rudikoff was published 12 years prior to Appellant's filing date; Adair 3 years prior; and Panka 6 years prior. Thus, none of these references are indicative of the state of the art in December 1994, the time this application was filed. Indeed, patents directed to production of bispecific antibodies

have routinely issued by the Office. (*See, e.g.,* U.S. Patent No. 4,474,893, cited on page 9, line 20 of the specification). Thus, contrary to the Examiner's assertion, at the time the pending application was filed, many of the problems associated with production of antibodies had been solved and these solutions were publicly available.

Even assuming, for the sake of argument only, that Rudikoff, Adair and/or Panka were representative of the state of the art as of Appellant's filing date, these references do not in any way establish unpredictability of methods involving the claimed bispecific antibodies to produce antibodies. In fact, none of these references address using bispecific antibodies at all, let alone using the particularly claimed bispecific antibodies to induce production of an antibody response. These references are a far cry away from establishing that the claimed methods are not enabled by Appellant's specification.

Thus, Rudikoff, Adair and Panka are not indicative of the state of the art at the time of filing and, moreover, are silent as to bispecific antibodies entirely. Therefore, these reference cannot serve as evidence that it would require undue experimentation to practice the invention as claimed. Discussions about CDRs in different antibodies does not rise to the level of establishing that the claimed invention is "unpredictable" or that it would require "undue experimentation" to practice the invention.

Dr. Wong also addressed Adair, Rudikoff and Panka and concluded that these references were not relevant to the claims on appeal:

> 9. It is further my opinion that Rudikoff, Adair or Panka do not accurately reflect the state of research in the field of bispecific antibodies as of December 1994. I base this opinion on the following facts. First, these references do not in any fashion address bispecific antibodies as used in the claimed methods. Rudikoff and Panka address how single amino acid substitutions in the CDR of an antibody can alter binding. Adair is directed to humanized antibody molecules (HAMs) having specificity for carcinoembryonic antigen (CEA) and to processes for their production using recombinant DNA technology. (See, Abstract). Nothing in these references is relevant to the claimed methods. Further, as all these references were published at least 3 years prior to December 1994, they are not representative of the state of the art at the time of filing.

In sum, the claimed methods are enabled by the specification as filed, and, accordingly, the various references cited by the Office are not relevant to the claimed invention and certainly do not establish unpredictability of the claimed methods.

(d) Declaratory evidence of record has not been properly considered

Despite the Office's failure to establish a *prima facie* case of non-enablement, Appellant has submitted still further evidence establishing that the specification fully enables the pending claims throughout their scope. The Office must consider evidence provided by the applicant that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See, e.g.,* PTO Training Manuals on Enablement, page 42; MPEP 716.09; *In re Brandstadter,* 179 USPQ 286 (CCPA 1973); *In re Ambruster,* 185 USPQ 152 (CCPA 1975); and *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). The evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art. PTO Training Manual on Enablement, page 42. In *In re Alton,* 37 USPQ2d 1578 (CAFC 1996), the Court of Appeals for the Federal Circuit held that it was error for the Examiner to dismiss with conclusory statements not only factual statements but also statements of opinion presented in Declarations made by qualified persons of ordinary skill in the art. The court commented that they were "aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner. [citation omitted]." *In re Alton,* 37 USPQ2d 1578 at 1583 n10.

In the present case, the Examiner has not considered the Declaratory evidence. In fact, Dr. Wong's Declaration completely rebuts the Examiner's conclusions that the claims on appeal are not enabled by the specification and that these claims are obvious over the cited references. Specifically, Dr. Wong notes the following facts and arrives at his conclusions using these facts.

First, bispecific antibodies as set forth in the claims (recognizing FcγRIII and a cancer antigen) were known at the time specification was filed. In particular, FcγRIII was a well-characterized isoform of the CD16 cell surface receptor. Similarly, a skilled artisan could have readily selected any suitable cancer antigen disclosed in the specification for use as the second

arm of the bispecific antibody. 2B1 is merely one example of a hybrid hybridoma capable of producing bispecific monoclonal antibody. *See,* Wong Declaration, paragraph 7, also citing page 10, lines 6-16 of the specification).

Second, it was known at the time of filing how to make bispecific antibodies and the specification also provides guidance in this regard. *See,* Wong Declaration, paragraph 7, citing page 9, line 12-28 of the specification.

Third, it was known how to administer bispecific antibodies to a subject. In addition, it was known how to test the subject to determine whether antibodies to the cancer antigen were elicited. *See,* Wong Declaration, paragraph 8.

On the basis of the foregoing, factual statements (further supported by references), Dr. Wong concludes that a skilled worker could have readily designed, made, tested and used a bispecific antibody falling within the scope of the claims:

> 10. Thus, it is my opinion that a skilled worker could have readily designed, made, tested and used a bispecific antibody falling within the scope of the claims. As noted above, bispecific antibodies were routinely made and administered. Similarly, assays for testing antibody production were routine in December 1994. The generation and testing of bispecific antibodies is described in Fanger et al. (1991) *Trends Biotechnol* 9(11):375-80 (Exhibit B) and Ring et al. "Breast Epithelial Antigens: Molecular Biology to Clinical Applications" (Exhibit C), as well as U.S. Patent Nos. 4,714,681 and 4,474,893 (Exhibit D). These and other references address the pertinent question at issue here -- whether bispecific antibodies that recognize FcγRIII and a cancer antigen can be made and used to produce antibodies against the cancer antigens following the teachings of the specification. These references plainly confirm that neither making bispecific antibodies nor testing antibody production in response to administration of these antibodies were unpredictable as of December 1994. Further, they are clearly representative of the high level of existing skill in the art and the fact that generation of bispecific antibodies was considered routine and entirely predictable in December 1994. In sum, to the skilled worker, making and using the claimed bispecific antibodies would have been routine and would have required little or no experimentation, particularly in light of the clear guidance in the specification regarding how to make, test and use bispecific antibodies as claimed.
>
> 11. In view of the foregoing facts regarding the routine nature of experimentation required to make, use and deliver bispecific antibodies directed against FcγRIII and a cancer antigen, the extensive direction provided by the

> specification, the straightforward nature of the claimed subject matter, the high level of the skilled worker, the sophistication of the art, and the predictability of the art, it is my unequivocal opinion that the specification enabled, in December 1994, a skilled worker to practice the methods as claimed.

Based on the teachings of the specification and the state of the art at the time of filing, Dr. Wong confirms that it would have required little or no experimentation for one skilled in the art to identify suitable bispecific antibodies and evaluate these antibodies for their ability to generate antibodies against a cancer antigen. (See, Wong Declaration, paragraphs 7-10).

Thus, the evidence of record conclusively contradicts the Examiner's assertions that it would have required undue experimentation to practice the claimed methods using antibodies other than 2B1. Accordingly, Appellant submits that the enablement rejections should be withdrawn.

2. *Prima facie* obviousness of claims 1-3, 8 and 15 has not been established

Claims 1-3, 8 and 15 were rejected under 35 U.S.C. § 103(a) (hereinafter "103") as allegedly obvious over Hsieh-Ma et al. (Cancer Research, 1992) or Weiner et al. (Cancer Research, 1993) or Ring et al. (Breast Epithelial Antigens, 1991) in view of Fanger et al. (Critical Reviews in Immunology, 1992) or Snider et al. (J. Exp. Med. 171:1957-1963, 1990). Collectively, Hseih-Ma, Weiner and Ring are referred to as the "primary references." In addition, claims 1-3, 5-8, and 15 also stand rejected as allegedly obvious over the primary references in view of Fanger or Snider and in further view of U.S. Patent No. 6,054,561.

In support of the rejections, the Examiner maintained that the primary references teach all the limitations of the claims except for antibody production to the second antigen. (Final Office Action, paragraph 6, page 6). Fanger and Snider were cited for alleging teaching that bispecific antibodies targeted to the APC cell antigens induce production of antibodies to the second antigen. (Final Office Action, paragraph 6, page 6). Further, in rejecting Appellant's previous arguments the Final Office Action stated:

> the burden of proof is upon Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibodies with the antibody and the 2B1 antibody of the prior art.

Appellant submits the Examiner has used prohibited hindsight reconstruction in making these rejections, as there is no teaching, suggestion or motivation within the cited references to support the rejection made by the Examiner. Additionally, the claims are patentable because of secondary considerations of non-obviousness.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The reference must teach all the limitations of the claimed invention and, moreover, suggests the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of along sought and difficult scientific goal was obvious" and *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.") Thus, the Board has previously acknowledged that disclosure of an isolated protein does not necessarily render obvious the same recombinantly produced protein. *See, e.g., Ex parte Goeddel,* 5 USPQ2d 1449 (BAPI, 1987).

Appellant submits that the Examiner has failed to make out a *prima facie* case of obviousness because no combination of the references teaches or suggests each and every element of the invention recited in claims 1, 3, 8 and 15. Further, there is simply no motivation within the references to arrive at the claimed invention.

(a) The references do not teach or suggest that a bispecific antibody could be used to induce antibodies to cancer antigens

To briefly reiterate, claims 1-3, 8 and 15 are all directed to methods of inducing **antibodies** to cancer antigens by administering the bispecific antibodies as claimed. Nowhere do

any of the references teach or suggest the induction of antibodies against cancer antigens using bispecific antibodies as claimed. Nor do these references provide any motivation or suggest the desirability of such methods. The failure of the cited references to suggest the claimed methods is also laid out in the Wong Declaration of record. There is simply no basis in the references for making an obviousness rejection and Appellant submits that it should be withdrawn.

Turning now to the Examiner's assertion that the burden in on Appellant to show that 2B1 bispecific antibody (disclosed in some of the references) would not have inherently induced antibodies to cancer antigens as claimed, Appellant submits that this is not the proper standard for determining obviousness. Indeed, it is well settled that, obviousness **cannot** be predicated on what is unknown:

> The inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. *In re Shetty, supra* quoting *In re Sporman,* 150 USPQ 449 (CCPA 1966).

In the pending case, it was certainly not known at the time of filing that the claimed bispecific antibodies would induce antibodies against cancer antigens. Dr. Wong is in accord:

> 12. It is further my opinion that the references cited in the Final Office Action do not describe, demonstrate or suggest the claimed methods. The application at issue discloses and claims methods of inducing an antibody response to a cancer antigen using a bispecific antibody. The bispecific antibody itself recognized FcγRIII and the cancer antigen. There is no disclosure in any of Hseih-Ma, Weiner, Ring, Fanger of Snider that would lead any scientist working in this area to conclude that bispecific antibodies would be useful in generating antibodies against cancer antigens. The fact that bispecific antibodies can have induce such antibodies was, in fact, a surprising finding made by the present inventors *after* all of the references were published, as noted on page 6, lines 24-28 of the specification:
>
> > It has now been found that administration of bispecific antibodies which recognize and bind FcγRIII and a second antigen can promote an immune response in humans to the second antigen. The immune response includes the formation of antibodies to the second antigen.

> Nowhere do any of the references report or test antibody production in response to the precisely-claimed subject matter. Accordingly, I do not believe that any combination of the cited references would lead one of skill in the art to the methods claimed by Applicant.

Thus, the Examiner has improper ignored the requirement that the claimed methods result in the induction of antibodies to the cancer antigen recognized by the second binding site of the bispecific antibody. Functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. (M.P.E.P. 2173.05(g) Functional Limitations, Eighth Edition). There is nothing inherently wrong with defining some part of an invention in functional terms and functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). Indeed, where the particular intended result (in this case production of antibodies to specified antigens) is a limitation of the pending claims it is entirely relevant to patentability. Accordingly, the requirement in these claims regarding the nature of immune response generated is entirely relevant the obviousness inquiry and establishes, along with the other evidence of record, that the claims are patentable over any combination of the cited references.

Here, the claims on appeal expressly recite that the claimed methods must result in the production of antibodies directed against the cancer antigen and, hence, this limitation is relevant to patentability. It is unacceptable for the Examiner to ignore this limitation and assert that any art related to the making or using of bispecific antibodies is relevant, much less than these references render the particularly claimed invention unpatentable. Likewise, the Examiner cannot ignore the legal axiom that obviousness cannot be based on what was allegedly inherent. Thus, when the proper legal standards of obviousness are applied, it is clear that the claimed methods, drawn to production of antibodies using bispecific antibodies, are in no way obvious over the cited references.

There is, in sum, no motivation provided by the cited references to arrive at methods of inducing antibodies to cancer antigens as recited in the appealed claims. The steps and results of

the claimed methods are precisely defined -- in the claims themselves, not in the references. None of the references teach that antibodies to cancer antigens would be induced by administration of the claimed bispecific antibodies. Therefore, Appellant respectfully requests that the rejection of these claims as allegedly obvious over the cited references be withdrawn, and that these claims be allowed.

(b) Declaratory evidence of record has not been properly considered

As with enablement, Appellant submits that the Declaration of Dr. Justin Wong has not been adequately considered with regard to obviousness. Indeed, Dr. Wong, an immunologist by training who works in the field of bispecific antibodies, concluded that the references cited by the Examiner did not render the pending claims unpatentable, stating that:

> 12. It is further my opinion that the references cited in the Final Office Action do not describe, demonstrate or suggest the claimed methods. The application at issue discloses and claims methods of inducing an antibody response to a cancer antigen using a bispecific antibody. The bispecific antibody itself recognized FcγRIII and the cancer antigen. There is no disclosure in any of Hseih-Ma, Weiner, Ring, Fanger of Snider that would lead any scientist working in this area to conclude that bispecific antibodies would be useful in generating antibodies against cancer antigens. ... Nowhere do any of the references report or test antibody production in response t22 the precisely-claimed subject matter. Accordingly, I do not believe that any combination of the cited references would lead one of skill in the art to the methods claimed by Applicant.

The Examiner has not adequately addressed this convincing factual evidence. When properly considered, Dr. Wong is yet another part of the factual record that conclusively contradicts the Examiner's assertions that any combination of the cited references renders the pending claims obvious.

3. While *prima facie* obviousness has not been established, additional factual evidence of record further supports the nonobviousness of the claimed methods

As discussed above and during prosecution of this application, the Examiner has not established the *prima facie* obviousness of the claimed methods because the cited references do not teach or suggest induction of an antibody response to the cancer antigen recognized by the second binding site of a bispecific antibody.

Since no *prima facie* case has been established, Appellant has no burden of coming forward with evidence positively establishing nonobviousness. *See, e.g., In re Rinehart* 189 USPQ 143 (CCPA 1976).

However, additional scientific evidence is in fact of record in the present case and that additional evidence further supports the nonobviousness of the presently claimed methods. For example, it is clear from the factual record that eliciting an antibody response to a cancer antigen was neither contemplated nor expected by those working in this field. As described in the specification:

> Thus far in research studying the efficacy of bispecific antibodies, localized tumor cell lysis has been observed in cellular and murine *in vivo* studies where the effector cells have been in close proximity to the tumor cells upon administration of the bispecific antibody. ...
>
> It has now been found that administration of bispecific antibodies which recognize and bind FcγRIII and a second antigen can promote an immune response in humans to the second antigen. The immune response includes the formation of antibodies to the second antigen. (page 5, lines 9-12 and page 6, lines 24-28 of the specification)

The Examples further indicate how the methods of the appealed claims result in unexpected production of antibodies to the cancer antigen. *See, e.g.,* Table 1 on page 27 of the specification.

In summary, although a *prima facie* case of obviousness has not been made out (and indeed the references contain no supporting basis), additional factual evidence or record in the present case lends even further support to the nonobviousness of the claimed methods.

4. Additional arguments regarding separately grouped claims

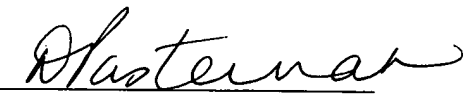
Each one of the preceding arguments is applicable to all of the separately grouped claims, *i.e.*, to each claim individually. For the sake of brevity, the arguments have been set out primarily as to independent claim 1. Claims 2-3, 8 and 15 contain all the elements of independent claim 1 and are, therefore, described, definite and patentable over the cited references for the reasons discussed in detail above. The dependent claims are also further limited in ways that are neither described nor suggested by the cited references, namely by further defining the elements of the claimed methods. The Examiner has not adequately explained why these claims are considered unpatentable over the cited references.

CONCLUSION

For the reasons stated above, Appellant respectfully submits that the pending claims are patentable over the art cited by the Examiner and, in addition, are described and sufficiently definite. Accordingly, Appellants request that the objections to the specification and the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: November 12, 2003

By: 

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CLAIMS ON APPEAL

1. (previously presented): A method of inducing production of antibodies against a cancer antigen, comprising the step of administering a bispecific antibody to the patient, said bispecific antibody comprising a first binding site capable of recognizing and binding a first antigen wherein said first antigen is FcγRIII and further comprising a second binding site capable of recognizing and binding a second antigen, in an amount sufficient to induce production of antibodies to said second antigen in said patient, wherein said second antigen is a cancer antigen selected from the group consisting of c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein and an antigen recognized by a monoclonal antibody produced by any of the following hybridomas: ATCC Accession Nos HB 11830, HB 11769, HB 11768, HB 10798, HB 10802, HB 8490, HB 8485, HB 8691, HB 11052, HB 10812, HB 8486, HB 10789, HB 8488, HB 8662, HB 8697, HB 10785, HB 10796, HB 10793, HB 11752, HB 10795, HB 10801, HB 11751 and HB 10794 and further wherein said second binding site comprises a binding site derived from a monoclonal antibody produced by a hybridoma selected from the group consisting of: HB11830, 452F2 (HB 10811), 741F8 (HB 10807), 759E3 (HB 10808), 454C11 (HB 8484), 387H9 (HB 10802), 113F1 (HB 8490), 317G5 (HB 8485, HB 8691), 34F2 (HB 11052), 650E2 (HB 10812), 35E6 (HB 11769), 266B2 (HB 8486), 106A10 (HB 10789), 260F9 (HB 8488 and HB 8662), 33F8 (HB 8697), 9C6 (HB 10785), 35E10 (HB 10796), 140A7 (HB 10798), 36H3 (HB11768), 788G6 (HB 8692), 200F9 (HB 10791), 697B3 (HB 10806), 120H7 (HB 10790), 203E2 (HB 10799), 254H9 (HB 10792), 245E7 (HB 8489), 2G3 (HB 8491), 369F10 (HB 8682), 15D3 (HB 11342), 421E8 (HB 10793), 310B7 (HB 11752), 32A1 (HB 10795), 219F3 (HB 10801), 42E7 (HB 11751), and 388D4 (HB 10794).

2. (original): The method according to claim 1, wherein said first binding site is a binding site derived from the monoclonal antibody produced from the 3G8 hybridoma.

3. (original): The method according to claim 1, wherein said second antigen is present in the patient.

4 to 7. (canceled).

8. (original): The method according to claim 1, wherein said bispecific antibody is produced by the hybrid hybridoma CRL 10197.

9 to 14. (canceled).

15. (original): The method according to claim 1, wherein said second antigen is not present in the patient upon first administration of the bispecific antibody.

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PATENT

CERTIFICATE OF MAILING PURSUANT TO 37 CFR § 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Appeal Brief – Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on November 12, 2003.

11/12/2003 Michelle Hobson

Date Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: A. Hollerhan
RING	Group Art Unit: 1642
Serial No.: 08/349,489	Confirmation No.: 6479
Filing Date: December 2, 1994	Customer No.: 20855
Title: METHOD OF PROMOTING AN IMMUNE RESPONSE WITH A BISPECIFIC ANTIBODY	

BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

INTRODUCTION

Appellant submits in triplicate his brief on appeal in accordance with 37 C.F.R. §1.192. All claims were finally rejected under 35 U.S.C. § 112, first paragraph (enablement), as well as under 35 U.S.C. § 103(a) in the Final Office Action, mailed December 18, 2002. A Response After Final was filed on March 18, 2003 and a Notice of Appeal was filed June 13, 2003, making a Brief on Appeal due on or before August 13, 2003. Appellant requests a three-month extension of time and attach the appropriate

fee, making a response due on or before November 13, 2003. Accordingly, this Brief is timely filed. Appellant respectfully requests that the decision of the Examiner be reversed and that the claims on appeal proceed to allowance.

TABLE OF CONTENTS

INTRODUCTION 1

I. REAL PARTY IN INTEREST 5

II. RELATED APPEALS AND INTERFERENCES 5

III. STATUS OF THE CLAIMS 5

IV. STATUS OF THE AMENDMENTS 5

V. SUMMARY OF THE CLAIMS 6

VI. ISSUES ON APPEAL 7

VII. GROUPING OF CLAIMS 7

VIII. ARGUMENTS 9

1. Undue Experimentation is not required to practice the claimed invention throughout their scope 9

(a) The specification enables the claimed methods throughout their scope 9

(b) The specification enables the of use bispecific antibodies other than 2B1 12

(c) The references do not establish unpredictability 14

(d) Declaratory evidence of record has not been properly considered. 16

2. *Prima facie* obviousness of claims 1-3, 8 and 15 has not been established 18

(a) The references do not teach or suggest that a bispecific antibody could be used to induce antibodies to cancer antigens 19

(b) Declaratory evidence of record has not been properly considered 22

3. While *prima facie* obviousness has not been established, additional factual evidence of record further supports the nonobviousness of the claimed methods 23

4. Additional Arguments Regarding Separately-Grouped Claims 24

CONCLUSION 25

APPENDIX A: LIST OF CLAIMS ON APPEAL

I. REAL PARTY IN INTEREST

Chiron Corporation, the assignee of record of the above-referenced patent application is the real party in interest in this matter.

II. RELATED APPEALS AND INTERFERENCES

Appellant is not aware of any related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 1-3, 8 and 15 are currently pending in the above-referenced case (hereinafter "the application"). The application was originally filed on December 2, 1994 with claims 1-15. Subject to a Restriction Requirement, claims 4 and 9-14 were withdrawn from consideration. A CPA was filed on May 11, 1999 and, on June 18, 1999, Appellant amended claim 6. An *In re Katz* Declaration was filed on December 22, 1999, removing various references. In an Amendment after Final, filed August 23, 2001, claim 1 was amended and claims 5-7 were canceled, without prejudice or disclaimer. A second CPA was filed on December 18, 2001 requesting entry of these amendments. In an amendment filed September 9, 2002, claim 1 was amended into its current form. No claims were amended in the Response filed After Final on March 18, 2003. Therefore, claims 1, 2, 3, 8 and 15 are pending as shown in Appendix A. All pending claims remain rejected under 35 U.S.C. § 112, first paragraph and under 35 U.S.C. § 103.

IV. STATUS OF THE AMENDMENTS

In response to the Examiner's Final Office Action mailed December 18, 2002, Appellant filed an Amendment After Final with an accompanying (unsigned) Rule 132 Declaration by Dr.

Justin Wong on March 18, 2003. The claims were not amended at this time and a signed copy of Dr. Wong's Declaration was submitted April 1, 2003. An Advisory Action has not been received. Thus, the pending claims are as set forth in Appendix A and all pending claims remained rejected for the reasons set forth in the Final Office Action.

V. SUMMARY OF THE CLAIMS

Appellant's claims are drawn generally to a method of inducing production of antibodies against a cancer antigen (page 6, lines 24-28). In particular, the method comprises administering a bispecific antibody, *i.e.*, an antibody that recognizes two antigens, to a patient in an amount sufficient to induce production of antibodies to the second antigen of the bispecific antibody (page 5, lines 19-20). Furthermore, the bispecific antibody used in these methods includes a first binding site capable of recognizing and binding FcγRIII and a second binding site capable of recognizing and binding a second antigen (page 6, lines 24-28). The second antigen (recognized by the second binding site of the bispecific antibody) is a cancer antigen, particularly c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein or an antigen recognized by a monoclonal antibody produced by any of the following hybridomas: ATCC Accession Nos HB 11830, HB 11769, HB 11768, HB 10798, HB 10802, HB 8490, HB 8485, HB 8691, HB 11052, HB 10812, HB 8486, HB 10789, HB 8488, HB 8662, HB 8697, HB 10785, HB 10796, HB 10793, HB 11752, HB 10795, HB 10801, HB 11751 and HB 10794 (page 5, line 27 to page 6, line 1; page 19, lines 11-23). In addition, the second binding site of the bispecific antibody comprises a binding site derived from a monoclonal antibody produced by a hybridoma selected from the group consisting of: HB11830, 452F2 (HB 10811), 741F8 (HB 10807), 759E3 (HB 10808), 454C11 (HB 8484), 387H9 (HB 10802), 113F1 (HB 8490), 317G5 (HB 8485, HB 8691), 34F2 (HB 11052), 650E2 (HB 10812), 35E6 (HB 11769), 266B2 (HB 8486), 106A10 (HB 10789), 260F9 (HB 8488 and HB 8662), 33F8 (HB 8697), 9C6 (HB 10785), 35E10 (HB 10796), 140A7 (HB 10798), 36H3 (HB11768), 788G6 (HB 8692), 200F9 (HB 10791), 697B3 (HB 10806), 120H7 (HB 10790), 203E2 (HB 10799), 254H9 (HB 10792), 245E7 (HB 8489), 2G3 (HB 8491),

369F10 (HB 8682), 15D3 (HB 11342), 421E8 (HB 10793), 310B7 (HB 11752), 32A1 (HB 10795), 219F3 (HB 10801), 42E7 (HB 11751), and 388D4 (HB 10794) (page 6, lines 1-11).

In addition, the first binding site (FcγRIII) can be, for example, a binding site derived from the monoclonal antibody produced from the 3G8 hybridoma (page 16, lines 13-16). Additionally, the second antigen can be present in the patient (page 5, lines 25-26) or, alternatively, not present in the patient upon first administration of the bispecific antibody (page 6, lines 20-21). The bispecific antibody used in these methods can be produced by the hybrid hybridoma CRL 10197 (page 20, lines 23-24).

Thus, the present claims methods of inducing an immune response to a cancer antigen by administering a bispecific antibody, where the second binding site of the bispecific antibody recognizes the cancer antigen (page 5, lines 19-24).

VI. ISSUES ON APPEAL

1. Whether the specification adequately enables the claims on appeal under the provisions of 35 U.S.C. § 112, first paragraph.

2. Whether the claims on appeal are obvious over Hsieh-Ma et al. (Cancer Research, 1992) or Weiner et al. (Cancer Research, 1993) or Ring et al. (Breast Epithelial Antigens, 1991) in view of Fanger et al. (Critical Reviews in Immunology, 1992) or Snider et al. (J. Exp. Med. 171:1957-1963, 1990).

VII. GROUPING OF CLAIMS

Claims 1, 2, 3, 8 and 15 are separately patentable, enabled and described by the application as filed. Therefore, these claims are divided into 5 separate groups:

(1) Claim 1: Independent claim 1 is directed to a method of inducing production of antibodies against a cancer antigen by administering a bispecific antibody to a subject. The

bispecific antibody comprises two binding sites -- one that recognizes FcγRIII and the other that recognizes a cancer antigen. The second binding site (and second antigen recognized by the second binding site) is further defined in terms of Accession Numbers and other identifiers.

(2) Claim 2: Claim 2 is directed to the method of claim 1 and further specifies that the first binding site of the bispecific antibody is derived from the monoclonal antibody produced from the 3G8 hybridoma.

(3) Claim 3: Claim 3 is directed to the method of claim 1 and further specifies that the second (cancer) antigen is present in the patient.

(4) Claim 8: Claim 8 is directed to the method of claim 1 and further specifies that the bispecific antibody is produced by the hybrid hybridoma CRL 10197.

(5) Claim 15: Claim 15 is directed to the method of claim 1 and further specifies that the second (cancer) antigen is not present in the patient upon first administration of the bispecific antibody.

VIII. ARGUMENTS

1. Undue Experimentation is not required to practice the claimed invention throughout their scope

The claims have been rejected as not enabled by the specification. Appellant submits that undue experimentation is not required to practice the claimed invention because the claims are enabled throughout their scope and, in addition, that the references cited as allegedly establishing unpredictability do no such thing. Moreover, the Examiner has improperly ignored declaratory evidence establishing that the disclosure, as filed, thoroughly enables the claimed invention.

(a) The specification enables the claimed methods throughout their scope

The Examiner has continued to allege that the specification does not enable one of skill in the art to practice the methods as claimed. The Examiner's position remains that:

> ...the specification, while being enabling for the bispecific antibody 2B1 and methods of inducing an immune response by administering the antibody, does not reasonably provide enablement for methods of inducing an immune response using any bispecific antibody which binds FcγRIII and c-erbB-2 where the arm that binds c-erbB2 is "derived from" any of the numerous monoclonal antibodies recited in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. (Final Office Action, page 3).

Thus, the Examiner continues to assert that the claims must be limited to methods using the hybridoma (2B1) set forth in the working examples disclosed in the specification. (*See,* Final Office Action, page 3).

Appellant submits that there is ample guidance in the specification regarding bispecific antibodies as set forth in independent claim 1 and use of these antibodies in the claimed methods. As such, the enablement requirement of 35 U.S.C. § 112, first paragraph has been satisfied.

As a threshold matter, Appellant notes that the claims are not drawn to methods using any and all bispecific antibodies to induce any and all immune response. In fact, as noted above in

the Summary of the Invention, each and every one of the pending claims requires that the bispecific antibody be directed to FcγRIII and a specified cancer antigen. (*See*, Summary above and Appendix A). Furthermore, each and every one of the claims requires that administration of the precisely defined bispecific antibodies result in the induction of antibodies to the cancer antigen in the patient. Therefore, the scope of the claims is not as broad as painted by the Examiner.

In addition to misrepresenting the scope of the claimed invention, Appellant also submits that the Examiner has not applied the proper legal standard of enablement in maintaining this rejection and, moreover, has improperly ignored additional evidence of record. Indeed, it is axiomatic that evidence as to the availability of techniques for discovering additional embodiments is entirely relevant to the enablement inquiry. (*See, e.g.,* M.P.E.P. § 2164.01 which states the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art, citing *United States v. Telectronics Inc.,* 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989)). Routine experimentation is not "undue" and does not establish non-enablement. (see, *e.g., In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988), citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976). The Office must consider evidence provided by the applicant that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See, e.g.,* PTO Training Manuals on Enablement, page 42; MPEP 716.09; *In re Brandstadter,* 179 USPQ 286 (CCPA 1973); *In re Ambruster,* 185 USPQ 152 (CCPA 1975); and *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). The evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art. PTO Training Manual on Enablement, page 42.

An applicant is under no legal obligation to exemplify each and every member of a claimed genus. Rather, for a claimed genus, representative examples together with a statement applicable to the genus as whole is sufficient to establish enablement if the skilled artisan would expect the claimed genus could be used in the manner set forth. *See, e.g.,* U.S. Patent and

Trademark Office's Training Materials on Enablement, p. 29. Simply put, the proper legal standard for determining enablement is whether the specification provides enough guidance as to the existence of methods and materials that allow one of skill in the art to practice the claimed invention without undue experimentation. (see, *e.g., In re Wands,* 8 USPQ2d at 1404, citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976)).

The present record plainly establishes one of skill in the art could practice the claimed invention without undue experimentation. The specification is replete with representative examples and statements applicable to the genus as a whole. In particular, Appellant plainly teaches how to identify and use bispecific antibodies that bind to FcγRIII and a cancer antigen, as recited in the claimed methods. Indeed, the Examiner has acknowledged enablement of the exemplified embodiment (*e.g.,* use of 2B1 to induce antibodies to a cancer antigen), for example, on page 2, of the Final Office Action. Thus, the application discloses that bispecific antibodies were known and had been used to induce local cellular immune responses. (Background). In addition, methods of making bispecific antibodies were also known. (*See*, for example, page 9 of the specification and pages 17-20 describing cancer antigens). Moreover, methods of administering bispecific antibodies to a subject are clearly disclosed, for example, on page 24 of the application. Furthermore, with respect to determining whether antibody responses to the cancer antigen are induced, such methods were both routine at the time of filing and disclosed in the specification, for instance in the Examples.

Appellant's specification also contains the requisite statements applicable to the genus as a whole to satisfy the enablement requirement, on, for example, page 6, lines 24-28, where the application states that "[i]t has now been found that administration of bispecific antibodies which recognize and bind FcγRIII and a second antigen can promote an immune response in humans to the second antigen" and in Example 3, where it states "[t]his example demonstrates the induction of an immune response by administration of a bispecific antibody such as 2B1." Thus, in light of Appellant's disclosure (including the state of the art at the time of filing), designing, making and using bispecific antibodies that recognize FcγRIII and a cancer antigen to elicit antibody

production is well within the purview of a skilled artisan. The claims are fully enabled the specification and Appellant respectfully submits that the rejection of the pending claims under section 112, first paragraph should be removed.

Dr. Wong, an immunologist working in the field of bispecific antibodies, reviewed Appellant's specification and claims on appeal and unequivocally concluded that the claims were not unduly broad and, in fact, the specification provided ample guidance to the skilled worker to practice the methods as claimed:

> 7. In December 1994, the quantity of experimentation required to make bispecific antibodies that recognized FcγRIII and a cancer antigen was quite low. At the time of filing and as described in the specification, FcγRIII was a well-characterized isoform of the CD16 cell surface receptor. (*See,* for example, page 10, lines 6-16). One working in this field could have readily selected suitable cancer antigens, for example as described in detail on pages 17-20. Also well known at the time of filing were techniques of producing bispecific antibodies and these standard procedures are described throughout the specification as filed, for example, on page 9, line 12-28 (including the references cited therein). Based on these extensive teachings regarding each of the antigens recognized by the claimed bispecific antibody and, additionally, the extensive teachings regarding production of bispecific antibodies, it is evident that a skilled worker would have easily produced bispecific antibodies which bound both FcγRIII and a cancer antigen. Thus, it is clear from the specification that 2B1 is merely one example of a hybrid hybridoma capable of producing bispecific monoclonal antibody. Therefore, it is my opinion that it would have required only routine experimentation for the skilled worker to make a bispecific antibody that recognized FcγRIII and a cancer antigen, as recited in the pending claims.

Thus, the specification's disclosure fully enables the claims on appeal throughout their scope.

(b) The specification enables the use bispecific antibodies other than 2B1

As noted above, the Examiner continues to assert that it would require undue experimentation to practice the claimed methods with any bispecific antibody except 2B1. (Final Office Action, page 3).

Appellant submits that the factual record makes it plain that 2B1 is an exemplary bispecific antibody, and, in view of the broad disclosure of the specification, the claims cannot be limited to the bispecific antibody exemplified in the application. It is axiomatic that working examples are never required to establish enablement. *See, In re Stahilevitz* 212 USPQ 561 (CCPA 1982), in which the CCPA held that broad claims to immunological methods were enabled by the specification as filed despite not disclosing even a single operative embodiment. Even in the chemical arts, an applicant is never required to exemplify multiple embodiments encompassed by the claims. *See, e.g., In re Angstadt,* 190 USPQ 214 (CCPA 1976). Here, the Examiner is improperly requiring the Appellant show, *a priori*, that every species disclosed in the specification is operable. This is not the proper test of enablement. Simply put, the enablement requirement of Section 112 cannot be used as a justification for limiting Appellant to the embodiments disclosed in the working examples, particularly in light of the fact that the specification describes, with specificity and detail, bispecific antibodies to be used in the claimed methods.

Furthermore, the notion that one of ordinary skill in the art must have reasonable assurance of obtaining an active claimed product has been emphatically rejected by the courts. *See, Angstadt* at 219. So long as it is clear that some species render a composition operative, the inclusion of some possible inoperative species does not invalidate the claim under paragraph 1, of 35 U.S.C. §112. *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, CCPA 1971; *Horton v. Stevens*, 7 USPQ2d 1245, 1247, Fed. Cir. 1988. Moreover, even evidence of the need for some experimentation does not invalidate a claim on ground of undue experimentation, nor does it fulfill the PTO's burden of proof. (*In re Angstadt* at 504; *In re Morehouse*, 545 F.2d 162, 165, 192 USPQ 29,32, CCPA 1976.)

For the reasons set forth above, including the routine nature of making bispecific antibodies and the detailed disclosure of the specification (including working examples), it is clear that one of ordinary skill in the art could practice the claimed methods of anti-cancer

antigen antibody induction using any of the particularly claimed bispecific antibodies (FcγRIII- and cancer antigen-specific), without undue experimentation.

Again, Dr. Wong in full agreement that the claims should not be limited to 2B1:

> 8. Furthermore, the specification provides working examples and additional significant direction for evaluating whether a FcγRIII-cancer antigen binding bispecific antibody could be used to elicit an antibody response to the cancer antigen. Those of us working in the field of bispecific antibodies are well versed in administration of antibodies and in the various tests for determining whether antibodies are elicited, for example using assays described on pages 24-29 of the specification. Examples present in the specification demonstrate such assays. (See, Examples 2 and 3). Furthermore, since preparing bispecific antibodies in December of 1994 was well within the purview of a skilled worker, even if a particular bispecific antibody were inoperable for some reason (*e.g.*, it did not elicit antibodies against the cancer antigen), the skilled worker would have readily used the molecule as a starting point in order to design bispecific antibodies with the desired characteristics.

In sum, the application as filed provides ample guidance regarding all the claimed elements. Accordingly, it would have been plain to the skilled artisan that Appellants was in possession of the claimed subject matter at the time the application was filed.

(c) The references do not establish unpredictability

In the Final Office Action, the Examiner also continued to assert that various references (Rudikoff, Adair and Panka) demonstrate the "unpredictability" of the claimed methods. *See,* page 5 of the Final Office Action. In citing these references, the Examiner asserted, "the specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claimed." (See, page 5, Final Office Action). The Examiner's position appears to be that, due to recognized variability of CDRs, the claimed methods are unpredictable.

Enablement and predictability are determined as of the time of filing. Here, Rudikoff was published 12 years prior to Appellant's filing date; Adair 3 years prior; and Panka 6 years prior. Thus, none of these references are indicative of the state of the art in December 1994, the time this application was filed. Indeed, patents directed to production of bispecific antibodies

have routinely issued by the Office. (*See, e.g.,* U.S. Patent No. 4,474,893, cited on page 9, line 20 of the specification). Thus, contrary to the Examiner's assertion, at the time the pending application was filed, many of the problems associated with production of antibodies had been solved and these solutions were publicly available.

Even assuming, for the sake of argument only, that Rudikoff, Adair and/or Panka were representative of the state of the art as of Appellant's filing date, these references do not in any way establish unpredictability of methods involving the claimed bispecific antibodies to produce antibodies. In fact, none of these references address using bispecific antibodies at all, let alone using the particularly claimed bispecific antibodies to induce production of an antibody response. These references are a far cry away from establishing that the claimed methods are not enabled by Appellant's specification.

Thus, Rudikoff, Adair and Panka are not indicative of the state of the art at the time of filing and, moreover, are silent as to bispecific antibodies entirely. Therefore, these reference cannot serve as evidence that it would require undue experimentation to practice the invention as claimed. Discussions about CDRs in different antibodies does not rise to the level of establishing that the claimed invention is "unpredictable" or that it would require "undue experimentation" to practice the invention.

Dr. Wong also addressed Adair, Rudikoff and Panka and concluded that these references were not relevant to the claims on appeal:

> 9. It is further my opinion that Rudikoff, Adair or Panka do not accurately reflect the state of research in the field of bispecific antibodies as of December 1994. I base this opinion on the following facts. First, these references do not in any fashion address bispecific antibodies as used in the claimed methods. Rudikoff and Panka address how single amino acid substitutions in the CDR of an antibody can alter binding. Adair is directed to humanized antibody molecules (HAMs) having specificity for carcinoembryonic antigen (CEA) and to processes for their production using recombinant DNA technology. (See, Abstract). Nothing in these references is relevant to the claimed methods. Further, as all these references were published at least 3 years prior to December 1994, they are not representative of the state of the art at the time of filing.

In sum, the claimed methods are enabled by the specification as filed, and, accordingly, the various references cited by the Office are not relevant to the claimed invention and certainly do not establish unpredictability of the claimed methods.

(d) Declaratory evidence of record has not been properly considered

Despite the Office's failure to establish a *prima facie* case of non-enablement, Appellant has submitted still further evidence establishing that the specification fully enables the pending claims throughout their scope. The Office must consider evidence provided by the applicant that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See, e.g.,* PTO Training Manuals on Enablement, page 42; MPEP 716.09; *In re Brandstadter,* 179 USPQ 286 (CCPA 1973); *In re Ambruster,* 185 USPQ 152 (CCPA 1975); and *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). The evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art. PTO Training Manual on Enablement, page 42. In *In re Alton,* 37 USPQ2d 1578 (CAFC 1996), the Court of Appeals for the Federal Circuit held that it was error for the Examiner to dismiss with conclusory statements not only factual statements but also statements of opinion presented in Declarations made by qualified persons of ordinary skill in the art. The court commented that they were "aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner. [citation omitted]." *In re Alton,* 37 USPQ2d 1578 at 1583 n10.

In the present case, the Examiner has not considered the Declaratory evidence. In fact, Dr. Wong's Declaration completely rebuts the Examiner's conclusions that the claims on appeal are not enabled by the specification and that these claims are obvious over the cited references. Specifically, Dr. Wong notes the following facts and arrives at his conclusions using these facts.

First, bispecific antibodies as set forth in the claims (recognizing FcγRIII and a cancer antigen) were known at the time specification was filed. In particular, FcγRIII was a well-characterized isoform of the CD16 cell surface receptor. Similarly, a skilled artisan could have readily selected any suitable cancer antigen disclosed in the specification for use as the second

arm of the bispecific antibody. 2B1 is merely one example of a hybrid hybridoma capable of producing bispecific monoclonal antibody. *See,* Wong Declaration, paragraph 7, also citing page 10, lines 6-16 of the specification).

Second, it was known at the time of filing how to make bispecific antibodies and the specification also provides guidance in this regard. *See,* Wong Declaration, paragraph 7, citing page 9, line 12-28 of the specification.

Third, it was known how to administer bispecific antibodies to a subject. In addition, it was known how to test the subject to determine whether antibodies to the cancer antigen were elicited. *See,* Wong Declaration, paragraph 8.

On the basis of the foregoing, factual statements (further supported by references), Dr. Wong concludes that a skilled worker could have readily designed, made, tested and used a bispecific antibody falling within the scope of the claims:

> 10. Thus, it is my opinion that a skilled worker could have readily designed, made, tested and used a bispecific antibody falling within the scope of the claims. As noted above, bispecific antibodies were routinely made and administered. Similarly, assays for testing antibody production were routine in December 1994. The generation and testing of bispecific antibodies is described in Fanger et al. (1991) *Trends Biotechnol* 9(11):375-80 (Exhibit B) and Ring et al. "Breast Epithelial Antigens: Molecular Biology to Clinical Applications" (Exhibit C), as well as U.S. Patent Nos. 4,714,681 and 4,474,893 (Exhibit D). These and other references address the pertinent question at issue here -- whether bispecific antibodies that recognize FcγRIII and a cancer antigen can be made and used to produce antibodies against the cancer antigens following the teachings of the specification. These references plainly confirm that neither making bispecific antibodies nor testing antibody production in response to administration of these antibodies were unpredictable as of December 1994. Further, they are clearly representative of the high level of existing skill in the art and the fact that generation of bispecific antibodies was considered routine and entirely predictable in December 1994. In sum, to the skilled worker, making and using the claimed bispecific antibodies would have been routine and would have required little or no experimentation, particularly in light of the clear guidance in the specification regarding how to make, test and use bispecific antibodies as claimed.
>
> 11. In view of the foregoing facts regarding the routine nature of experimentation required to make, use and deliver bispecific antibodies directed against FcγRIII and a cancer antigen, the extensive direction provided by the

> specification, the straightforward nature of the claimed subject matter, the high level of the skilled worker, the sophistication of the art, and the predictability of the art, it is my unequivocal opinion that the specification enabled, in December 1994, a skilled worker to practice the methods as claimed.

Based on the teachings of the specification and the state of the art at the time of filing, Dr. Wong confirms that it would have required little or no experimentation for one skilled in the art to identify suitable bispecific antibodies and evaluate these antibodies for their ability to generate antibodies against a cancer antigen. (See, Wong Declaration, paragraphs 7-10).

Thus, the evidence of record conclusively contradicts the Examiner's assertions that it would have required undue experimentation to practice the claimed methods using antibodies other than 2B1. Accordingly, Appellant submits that the enablement rejections should be withdrawn.

2. *Prima facie* obviousness of claims 1-3, 8 and 15 has not been established

Claims 1-3, 8 and 15 were rejected under 35 U.S.C. § 103(a) (hereinafter "103") as allegedly obvious over Hsieh-Ma et al. (Cancer Research, 1992) or Weiner et al. (Cancer Research, 1993) or Ring et al. (Breast Epithelial Antigens, 1991) in view of Fanger et al. (Critical Reviews in Immunology, 1992) or Snider et al. (J. Exp. Med. 171:1957-1963, 1990). Collectively, Hseih-Ma, Weiner and Ring are referred to as the "primary references." In addition, claims 1-3, 5-8, and 15 also stand rejected as allegedly obvious over the primary references in view of Fanger or Snider and in further view of U.S. Patent No. 6,054,561.

In support of the rejections, the Examiner maintained that the primary references teach all the limitations of the claims except for antibody production to the second antigen. (Final Office Action, paragraph 6, page 6). Fanger and Snider were cited for alleging teaching that bispecific antibodies targeted to the APC cell antigens induce production of antibodies to the second antigen. (Final Office Action, paragraph 6, page 6). Further, in rejecting Appellant's previous arguments the Final Office Action stated:

> the burden of proof is upon Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibodies with the antibody and the 2B1 antibody of the prior art.

Appellant submits the Examiner has used prohibited hindsight reconstruction in making these rejections, as there is no teaching, suggestion or motivation within the cited references to support the rejection made by the Examiner. Additionally, the claims are patentable because of secondary considerations of non-obviousness.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The reference must teach all the limitations of the claimed invention and, moreover, suggests the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of along sought and difficult scientific goal was obvious" and *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.") Thus, the Board has previously acknowledged that disclosure of an isolated protein does not necessarily render obvious the same recombinantly produced protein. *See, e.g., Ex parte Goeddel,* 5 USPQ2d 1449 (BAPI, 1987).

Appellant submits that the Examiner has failed to make out a *prima facie* case of obviousness because no combination of the references teaches or suggests each and every element of the invention recited in claims 1, 3, 8 and 15. Further, there is simply no motivation within the references to arrive at the claimed invention.

(a) The references do not teach or suggest that a bispecific antibody could be used to induce antibodies to cancer antigens

To briefly reiterate, claims 1-3, 8 and 15 are all directed to methods of inducing **antibodies** to cancer antigens by administering the bispecific antibodies as claimed. Nowhere do

any of the references teach or suggest the induction of antibodies against cancer antigens using bispecific antibodies as claimed. Nor do these references provide any motivation or suggest the desirability of such methods. The failure of the cited references to suggest the claimed methods is also laid out in the Wong Declaration of record. There is simply no basis in the references for making an obviousness rejection and Appellant submits that it should be withdrawn.

Turning now to the Examiner's assertion that the burden in on Appellant to show that 2B1 bispecific antibody (disclosed in some of the references) would not have inherently induced antibodies to cancer antigens as claimed, Appellant submits that this is not the proper standard for determining obviousness. Indeed, it is well settled that, obviousness **cannot** be predicated on what is unknown:

> The inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. *In re Shetty, supra* quoting *In re Sporman,* 150 USPQ 449 (CCPA 1966).

In the pending case, it was certainly not known at the time of filing that the claimed bispecific antibodies would induce antibodies against cancer antigens. Dr. Wong is in accord:

> 12. It is further my opinion that the references cited in the Final Office Action do not describe, demonstrate or suggest the claimed methods. The application at issue discloses and claims methods of inducing an antibody response to a cancer antigen using a bispecific antibody. The bispecific antibody itself recognized FcγRIII and the cancer antigen. There is no disclosure in any of Hseih-Ma, Weiner, Ring, Fanger of Snider that would lead any scientist working in this area to conclude that bispecific antibodies would be useful in generating antibodies against cancer antigens. The fact that bispecific antibodies can have induce such antibodies was, in fact, a surprising finding made by the present inventors *after* all of the references were published, as noted on page 6, lines 24-28 of the specification:
>
> > It has now been found that administration of bispecific antibodies which recognize and bind FcγRIII and a second antigen can promote an immune response in humans to the second antigen. The immune response includes the formation of antibodies to the second antigen.

> Nowhere do any of the references report or test antibody production in response to the precisely-claimed subject matter. Accordingly, I do not believe that any combination of the cited references would lead one of skill in the art to the methods claimed by Applicant.

Thus, the Examiner has improper ignored the requirement that the claimed methods result in the induction of antibodies to the cancer antigen recognized by the second binding site of the bispecific antibody. Functional limitation must be evaluated and considered, just like any other limitation of the claim, for what it fairly conveys to a person of ordinary skill in the pertinent art in the context in which it is used. (M.P.E.P. 2173.05(g) Functional Limitations, Eighth Edition). There is nothing inherently wrong with defining some part of an invention in functional terms and functional language does not, in and of itself, render a claim improper. *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). Indeed, where the particular intended result (in this case production of antibodies to specified antigens) is a limitation of the pending claims it is entirely relevant to patentability. Accordingly, the requirement in these claims regarding the nature of immune response generated is entirely relevant the obviousness inquiry and establishes, along with the other evidence of record, that the claims are patentable over any combination of the cited references.

Here, the claims on appeal expressly recite that the claimed methods must result in the production of antibodies directed against the cancer antigen and, hence, this limitation is relevant to patentability. It is unacceptable for the Examiner to ignore this limitation and assert that any art related to the making or using of bispecific antibodies is relevant, much less than these references render the particularly claimed invention unpatentable. Likewise, the Examiner cannot ignore the legal axiom that obviousness cannot be based on what was allegedly inherent. Thus, when the proper legal standards of obviousness are applied, it is clear that the claimed methods, drawn to production of antibodies using bispecific antibodies, are in no way obvious over the cited references.

There is, in sum, no motivation provided by the cited references to arrive at methods of inducing antibodies to cancer antigens as recited in the appealed claims. The steps and results of

the claimed methods are precisely defined -- in the claims themselves, not in the references. None of the references teach that antibodies to cancer antigens would be induced by administration of the claimed bispecific antibodies. Therefore, Appellant respectfully requests that the rejection of these claims as allegedly obvious over the cited references be withdrawn, and that these claims be allowed.

(b) Declaratory evidence of record has not been properly considered

As with enablement, Appellant submits that the Declaration of Dr. Justin Wong has not been adequately considered with regard to obviousness. Indeed, Dr. Wong, an immunologist by training who works in the field of bispecific antibodies, concluded that the references cited by the Examiner did not render the pending claims unpatentable, stating that:

> 12. It is further my opinion that the references cited in the Final Office Action do not describe, demonstrate or suggest the claimed methods. The application at issue discloses and claims methods of inducing an antibody response to a cancer antigen using a bispecific antibody. The bispecific antibody itself recognized FcγRIII and the cancer antigen. There is no disclosure in any of Hseih-Ma, Weiner, Ring, Fanger of Snider that would lead any scientist working in this area to conclude that bispecific antibodies would be useful in generating antibodies against cancer antigens. ... Nowhere do any of the references report or test antibody production in response t22 the precisely-claimed subject matter. Accordingly, I do not believe that any combination of the cited references would lead one of skill in the art to the methods claimed by Applicant.

The Examiner has not adequately addressed this convincing factual evidence. When properly considered, Dr. Wong is yet another part of the factual record that conclusively contradicts the Examiner's assertions that any combination of the cited references renders the pending claims obvious.

3. While *prima facie* obviousness has not been established, additional factual evidence of record further supports the nonobviousness of the claimed methods

As discussed above and during prosecution of this application, the Examiner has not established the *prima facie* obviousness of the claimed methods because the cited references do not teach or suggest induction of an antibody response to the cancer antigen recognized by the second binding site of a bispecific antibody.

Since no *prima facie* case has been established, Appellant has no burden of coming forward with evidence positively establishing nonobviousness. *See, e.g., In re Rinehart* 189 USPQ 143 (CCPA 1976).

However, additional scientific evidence is in fact of record in the present case and that additional evidence further supports the nonobviousness of the presently claimed methods. For example, it is clear from the factual record that eliciting an antibody response to a cancer antigen was neither contemplated nor expected by those working in this field. As described in the specification:

> Thus far in research studying the efficacy of bispecific antibodies, localized tumor cell lysis has been observed in cellular and murine *in vivo* studies where the effector cells have been in close proximity to the tumor cells upon administration of the bispecific antibody. ...
>
> It has now been found that administration of bispecific antibodies which recognize and bind FcγRIII and a second antigen can promote an immune response in humans to the second antigen. The immune response includes the formation of antibodies to the second antigen. (page 5, lines 9-12 and page 6, lines 24-28 of the specification)

The Examples further indicate how the methods of the appealed claims result in unexpected production of antibodies to the cancer antigen. *See, e.g.,* Table 1 on page 27 of the specification.

In summary, although a *prima facie* case of obviousness has not been made out (and indeed the references contain no supporting basis), additional factual evidence or record in the present case lends even further support to the nonobviousness of the claimed methods.

4. Additional arguments regarding separately grouped claims

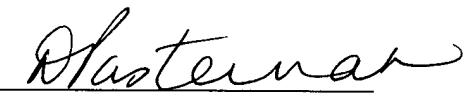
Each one of the preceding arguments is applicable to all of the separately grouped claims, *i.e.*, to each claim individually. For the sake of brevity, the arguments have been set out primarily as to independent claim 1. Claims 2-3, 8 and 15 contain all the elements of independent claim 1 and are, therefore, described, definite and patentable over the cited references for the reasons discussed in detail above. The dependent claims are also further limited in ways that are neither described nor suggested by the cited references, namely by further defining the elements of the claimed methods. The Examiner has not adequately explained why these claims are considered unpatentable over the cited references.

CONCLUSION

For the reasons stated above, Appellant respectfully submits that the pending claims are patentable over the art cited by the Examiner and, in addition, are described and sufficiently definite. Accordingly, Appellants request that the objections to the specification and the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: November 12, 2003

By: 

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CLAIMS ON APPEAL

1. (previously presented): A method of inducing production of antibodies against a cancer antigen, comprising the step of administering a bispecific antibody to the patient, said bispecific antibody comprising a first binding site capable of recognizing and binding a first antigen wherein said first antigen is FcγRIII and further comprising a second binding site capable of recognizing and binding a second antigen, in an amount sufficient to induce production of antibodies to said second antigen in said patient, wherein said second antigen is a cancer antigen selected from the group consisting of c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein and an antigen recognized by a monoclonal antibody produced by any of the following hybridomas: ATCC Accession Nos HB 11830, HB 11769, HB 11768, HB 10798, HB 10802, HB 8490, HB 8485, HB 8691, HB 11052, HB 10812, HB 8486, HB 10789, HB 8488, HB 8662, HB 8697, HB 10785, HB 10796, HB 10793, HB 11752, HB 10795, HB 10801, HB 11751 and HB 10794 and further wherein said second binding site comprises a binding site derived from a monoclonal antibody produced by a hybridoma selected from the group consisting of: HB11830, 452F2 (HB 10811), 741F8 (HB 10807), 759E3 (HB 10808), 454C11 (HB 8484), 387H9 (HB 10802), 113F1 (HB 8490), 317G5 (HB 8485, HB 8691), 34F2 (HB 11052), 650E2 (HB 10812), 35E6 (HB 11769), 266B2 (HB 8486), 106A10 (HB 10789), 260F9 (HB 8488 and HB 8662), 33F8 (HB 8697), 9C6 (HB 10785), 35E10 (HB 10796), 140A7 (HB 10798), 36H3 (HB11768), 788G6 (HB 8692), 200F9 (HB 10791), 697B3 (HB 10806), 120H7 (HB 10790), 203E2 (HB 10799), 254H9 (HB 10792), 245E7 (HB 8489), 2G3 (HB 8491), 369F10 (HB 8682), 15D3 (HB 11342), 421E8 (HB 10793), 310B7 (HB 11752), 32A1 (HB 10795), 219F3 (HB 10801), 42E7 (HB 11751), and 388D4 (HB 10794).

2. (original): The method according to claim 1, wherein said first binding site is a binding site derived from the monoclonal antibody produced from the 3G8 hybridoma.

3. (original): The method according to claim 1, wherein said second antigen is present in the patient.

4 to 7. (canceled).

8. (original): The method according to claim 1, wherein said bispecific antibody is produced by the hybrid hybridoma CRL 10197.

9 to 14. (canceled).

15. (original): The method according to claim 1, wherein said second antigen is not present in the patient upon first administration of the bispecific antibody.